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(*S*)-2-Azaniumyl-2-methyl-3-phenylpropanoate monohydrate

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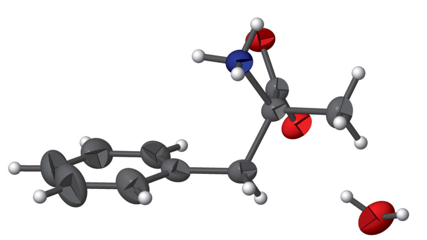
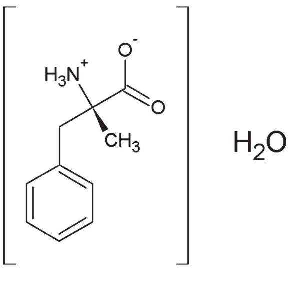
Structural data: full structural data are available from iucrdata.iucr.org

The title compound, $C_{10}H_{13}NO_2 \cdot H_2O$, crystallizes in a zwitterionic form as a monohydrate, involving the propylbenzene group with a *trans* conformation. It is a non-natural amino acid, and has attracted attention as an inhibitor of phenylalanine hydroxylase. In the crystal, molecules are linked by N—H···O hydrogen bonds, forming *C*(5) chains along the *c*-axis direction. Two chains are linked by another N—H···O hydrogen bond, forming an $R_3^3(11)$ ring motif. Further O—H···O hydrogen bonds link these motifs *via* the water molecules, to form a three-dimensional framework.

3D view



Chemical scheme



Structure description

Solid-phase synthesis is now the accepted method to synthesize peptides, in which protected natural or non-natural amino acids are widely used; for example, 2-methylphenylalanine (MePhe), a non-natural amino acid. At first, it attracted attention as a substrate analogue and an inhibitor of phenylalanine hydroxylase (EC 1.14.16.1: phenylalanine 4-monooxygenase), related to phenylketonuria (PKU), a genetic disorder (Greengard *et al.*, 1976; Binek *et al.*, 1981). Despite the biological and pharmaceutical interest, only a few crystal structures for 2-methyl-substituted phenylalanine derivatives have been reported, for example (*R*)-α-MePheOMe·HCl·H_2O (QABCAX; Crisma *et al.*, 1997), (*RS*)-α-MeTyr (DMTYRS; Gaudestad *et al.*, 1976) or (*S*)-α-MeDOPA·1.5H_2O (COSGUM; Neuman *et al.*, 1984).

In the title compound (Fig. 1, CAS No. 23239–35-2 for the non-hydrated molecule), the molecule has a conformation like a cross, in which the propylbenzene group has a *trans* conformation [torsion angle C10—C2—C3—C4: τ = 167.9 (2)°]. A similar conformation is found in other 2-methyl-substituted amino acids, for example, *iso*Val monohydrate, CISNUP [τ = 177.0 (3)°; Butcher *et al.*, 2013] and DMTYRS [τ = −176.58 (1)°], while the *cis* conformation is observed in other cases, as in QABCAX. This slightly distorted

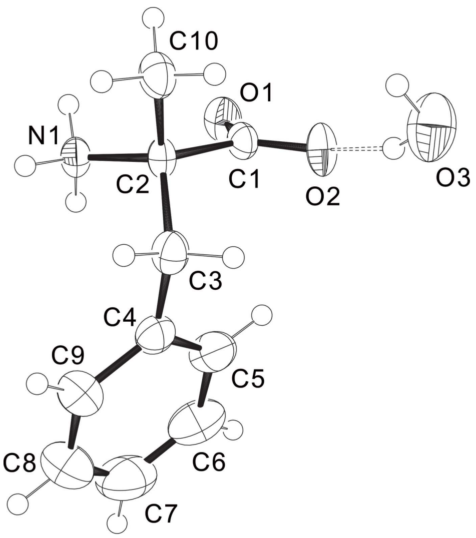


Figure 1
A view of the molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level. The dashed line indicates the intermolecular O—H···O hydrogen bond (see Table 1, entry 3).

conformation is also comparable to that found in the crystal structures of phenylalanine derivatives, for example in L-Phe monohydrate (GOFWOP; Williams *et al.*, 2013).

In the crystal, molecules are linked by N—H···O hydrogen bonds, forming $C(5)$ chains along the *c*-axis direction (Table 1, entry 1). Two chains are linked by another N—H···O hydrogen bond, forming $R_3^3(11)$ rings, approximately parallel to the *bc* plane (Fig. 2). Further O—H···O and N—H···O hydrogen bonds link the layers of *R* rings *via* the water molecules, forming a three-dimensional framework (Table 1 and Fig. 3).

The methyl groups are surrounded by the hydrophilic planes and are arranged in a columnar structure (Fig. 3), similar to that of 2-MeAsp (NUPVUR; Fujii, 2015). The hydrophilic layers present a honeycomb arrangement, and are well separated from the hydrophobic layers along the *b*-axis direction (Fig. 3).

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*C*···O2[i]	0.93 (3)	1.83 (3)	2.7642 (18)	175 (3)
N1—H1*B*···O1[ii]	0.91 (2)	1.99 (2)	2.8581 (18)	160.6 (19)
O3—H11*A*···O2	0.87 (2)	2.06 (2)	2.897 (2)	160 (3)
O3—H11*B*···O1[iii]	0.91 (2)	1.92 (2)	2.825 (2)	178 (4)
N1—H1*A*···O3[iv]	0.96 (3)	2.40 (3)	3.050 (2)	124.9 (18)

Symmetry codes: (i) $x, y, z+1$; (ii) $-x+\frac{3}{2}, -y, z+\frac{1}{2}$; (iii) $x-1, y, z$; (iv) $x+1, y, z+1$.

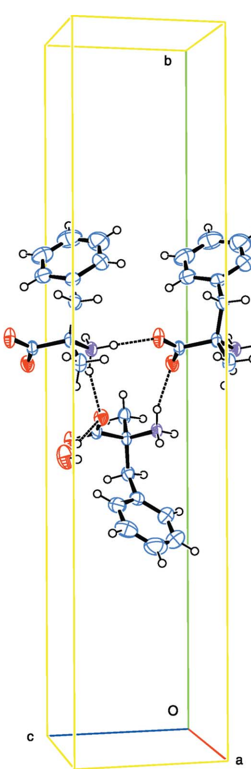


Figure 2
A view of the crystal packing of the title compound. Dashed lines indicate the N—H···O and O—H···O hydrogen bonds (see Table 1).

Synthesis and crystallization

The title compound was purchased from Nagase–Sangyo Co. Ltd. The absolute configuration could not be established by anomalous-dispersion effects. The *S* enantiomer has been chosen by referring to the sign of the known polarity in the synthetic procedure (Yamada *et al.*, 1969). Rod-like colourless crystals of the title compound were obtained by vapour-phase diffusion of an aqueous ethanol–chloroform solvent mixture at room temperature.

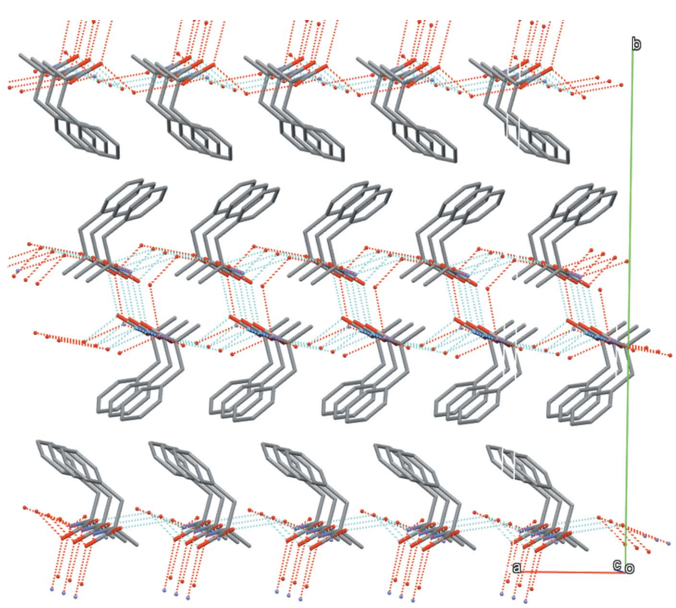


Figure 3
A view along the *c* axis of the crystal packing of the title compound. Dashed lines indicate the O—H···O and N—H···O hydrogen bonds (see Table 1).

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{10}H_{13}NO_2 \cdot H_2O$
M_r	197.23
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	297
a, b, c (Å)	6.1146 (9), 28.3272 (10), 5.9614 (8)
V (Å^3)	1032.6 (2)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.77
Crystal size (mm)	0.4 × 0.2 × 0.2
Data collection	
Diffractometer	Enraf–Nonius CAD-4-turbo
Absorption correction	ψ scan (North *et al.*, 1968)
T_{min}, T_{max}	0.750, 0.860
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	1490, 1448, 1384
R_{int}	0.071
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.623
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.029, 0.082, 1.08
No. of reflections	1448
No. of parameters	149
No. of restraints	2
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.16, −0.18

Computer programs: *CAD-4 Software* (Enraf–Nonius, 1994), *XCAD4* (Harms & Wocadlo, 1995), *SHELXS97* (Sheldrick, 2008), *SHELXL2014* (Sheldrick, 2015),

Acknowledgements

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full crystallographic data

IUCrData (2016). **1**, x161516 [https://doi.org/10.1107/S2414314616015169]

(*S*)-2-Azaniumyl-2-methyl-3-phenylpropanoate monohydrate

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(*S*)-2-Azaniumyl-2-methyl-3-phenylpropanoate monohydrate

Crystal data

$C_{10}H_{13}NO_2{\cdot}H_2O$
M_r = 197.23
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
a = 6.1146 (9) Å
b = 28.3272 (10) Å
c = 5.9614 (8) Å
V = 1032.6 (2) Å^3
Z = 4
F(000) = 424
D_x = 1.269 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 25 reflections
θ = 28–35°
μ = 0.77 mm^{-1}
T = 297 K
Rod, colorless
0.4 × 0.2 × 0.2 mm

Data collection

Enraf–Nonius CAD-4-turbo diffractometer
Radiation source: Enraf–Nonius FR590
Graphite monochromator
non–profiled $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.750, T_{max} = 0.860
1490 measured reflections
1448 independent reflections
1384 reflections with $I > 2\sigma(I)$
R_{int} = 0.071
θ_{max} = 73.9°, θ_{min} = 3.1°
$h = -1{\rightarrow}7$
$k = 0{\rightarrow}35$
$l = -7{\rightarrow}0$
3 standard reflections every 60 min
intensity decay: 1%

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.082
S = 1.08
1448 reflections
149 parameters
2 restraints
0 constraints
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0485P)^2 + 0.1286P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ < 0.001
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: SHELXL2014 (Sheldrick, 2015), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.0047 (9)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
C10	0.2812 (3)	0.03959 (6)	0.5984 (3)	0.0381 (4)
H10A	0.3235	0.0072	0.5798	0.057*

H10B	0.1725	0.0476	0.4886	0.057*
H10C	0.222	0.0441	0.7461	0.057*
N1	0.6435 (2)	0.05862 (5)	0.7456 (2)	0.0301 (3)
O3	0.0250 (3)	0.09096 (7)	0.0372 (3)	0.0624 (4)
C1	0.5807 (3)	0.06044 (5)	0.3360 (2)	0.0280 (3)
C2	0.4804 (3)	0.07123 (5)	0.5680 (2)	0.0271 (3)
C3	0.4175 (3)	0.12352 (5)	0.5933 (3)	0.0343 (4)
H3A	0.3305	0.1327	0.4644	0.041*
H3B	0.3261	0.1269	0.7254	0.041*
C4	0.6074 (3)	0.15712 (5)	0.6137 (3)	0.0380 (4)
C5	0.7560 (4)	0.16373 (6)	0.4415 (4)	0.0473 (5)
H5	0.7382	0.1473	0.3077	0.057*
C6	0.9312 (4)	0.19445 (7)	0.4654 (5)	0.0618 (6)
H6	1.0315	0.1979	0.3494	0.074*
C7	0.9564 (5)	0.21965 (8)	0.6600 (5)	0.0756 (8)
H7	1.0724	0.2407	0.6755	0.091*
C8	0.8094 (6)	0.21368 (8)	0.8318 (5)	0.0786 (8)
H8	0.8264	0.2307	0.9639	0.094*
C9	0.6365 (4)	0.18263 (7)	0.8105 (4)	0.0565 (6)
H9	0.5389	0.1788	0.9287	0.068*
O1	0.75798 (19)	0.03832 (4)	0.3320 (2)	0.0377 (3)
O2	0.4743 (2)	0.07410 (5)	0.16925 (18)	0.0402 (3)
H1A	0.778 (4)	0.0757 (8)	0.733 (4)	0.054 (6)*
H1B	0.683 (4)	0.0279 (8)	0.739 (3)	0.043 (5)*
H1C	0.579 (5)	0.0644 (7)	0.885 (4)	0.055 (6)*
H11A	0.158 (4)	0.0929 (12)	0.091 (6)	0.111 (12)*
H11B	−0.058 (6)	0.0735 (11)	0.131 (6)	0.124 (14)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C10	0.0367 (8)	0.0508 (8)	0.0267 (7)	−0.0065 (8)	0.0027 (7)	−0.0004 (7)
N1	0.0343 (7)	0.0354 (7)	0.0207 (6)	0.0039 (6)	−0.0012 (6)	0.0007 (5)
O3	0.0504 (9)	0.0922 (12)	0.0447 (8)	0.0064 (9)	0.0081 (8)	0.0098 (8)
C1	0.0313 (7)	0.0329 (7)	0.0199 (6)	−0.0011 (6)	0.0032 (7)	−0.0014 (5)
C2	0.0288 (8)	0.0352 (7)	0.0173 (6)	0.0033 (6)	0.0005 (6)	0.0003 (5)
C3	0.0356 (8)	0.0386 (7)	0.0286 (7)	0.0082 (7)	0.0030 (7)	−0.0002 (6)
C4	0.0464 (9)	0.0305 (7)	0.0371 (8)	0.0069 (7)	−0.0009 (8)	0.0029 (6)
C5	0.0531 (11)	0.0382 (8)	0.0507 (10)	0.0007 (8)	0.0072 (11)	0.0034 (8)
C6	0.0539 (12)	0.0495 (10)	0.0819 (16)	−0.0035 (10)	0.0101 (14)	0.0158 (10)
C7	0.0731 (16)	0.0520 (11)	0.102 (2)	−0.0188 (12)	−0.0224 (19)	0.0098 (13)
C8	0.108 (2)	0.0584 (12)	0.0692 (15)	−0.0206 (15)	−0.0236 (19)	−0.0094 (12)
C9	0.0775 (15)	0.0477 (9)	0.0443 (10)	−0.0044 (11)	−0.0012 (13)	−0.0067 (8)
O1	0.0375 (6)	0.0449 (6)	0.0306 (5)	0.0102 (5)	0.0062 (6)	−0.0029 (5)
O2	0.0383 (7)	0.0628 (7)	0.0194 (5)	0.0065 (6)	0.0007 (5)	0.0011 (5)

Geometric parameters (Å, º)

C10—C2	1.523 (2)	C3—C4	1.506 (3)
C10—H10A	0.96	C3—H3A	0.97
C10—H10B	0.96	C3—H3B	0.97
C10—H10C	0.96	C4—C5	1.383 (3)
N1—C2	1.4983 (19)	C4—C9	1.389 (2)
N1—H1A	0.96 (3)	C5—C6	1.388 (3)
N1—H1B	0.91 (2)	C5—H5	0.93
N1—H1C	0.93 (3)	C6—C7	1.371 (4)
O3—H11A	0.87 (2)	C6—H6	0.93
O3—H11B	0.91 (2)	C7—C8	1.373 (4)
C1—O2	1.2497 (19)	C7—H7	0.93
C1—O1	1.252 (2)	C8—C9	1.381 (4)
C1—C2	1.5435 (19)	C8—H8	0.93
C2—C3	1.538 (2)	C9—H9	0.93
C2—C10—H10A	109.5	C4—C3—H3A	108.5
C2—C10—H10B	109.5	C2—C3—H3A	108.5
H10A—C10—H10B	109.5	C4—C3—H3B	108.5
C2—C10—H10C	109.5	C2—C3—H3B	108.5
H10A—C10—H10C	109.5	H3A—C3—H3B	107.5
H10B—C10—H10C	109.5	C5—C4—C9	118.15 (19)
C2—N1—H1A	113.3 (14)	C5—C4—C3	122.14 (15)
C2—N1—H1B	112.2 (14)	C9—C4—C3	119.71 (17)
H1A—N1—H1B	104.6 (19)	C4—C5—C6	121.1 (2)
C2—N1—H1C	107.7 (16)	C4—C5—H5	119.5
H1A—N1—H1C	110 (2)	C6—C5—H5	119.5
H1B—N1—H1C	108.8 (19)	C7—C6—C5	120.0 (2)
H11A—O3—H11B	109 (3)	C7—C6—H6	120
O2—C1—O1	126.21 (14)	C5—C6—H6	120
O2—C1—C2	116.37 (13)	C6—C7—C8	119.5 (2)
O1—C1—C2	117.41 (13)	C6—C7—H7	120.2
N1—C2—C10	107.93 (12)	C8—C7—H7	120.2
N1—C2—C3	109.06 (12)	C7—C8—C9	120.7 (2)
C10—C2—C3	110.82 (14)	C7—C8—H8	119.6
N1—C2—C1	108.74 (12)	C9—C8—H8	119.6
C10—C2—C1	107.95 (12)	C8—C9—C4	120.5 (2)
C3—C2—C1	112.22 (12)	C8—C9—H9	119.8
C4—C3—C2	115.10 (14)	C4—C9—H9	119.8

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*C*···O2^{i}	0.93 (3)	1.83 (3)	2.7642 (18)	175 (3)
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O3—H11*B*···O1^{iii}	0.91 (2)	1.92 (2)	2.825 (2)	178 (4)

C10—H10*C*···O3^{i}	0.96	2.5	3.378 (2)	153
N1—H1*A*···O3^{iv}	0.96 (3)	2.40 (3)	3.050 (2)	124.9 (18)

Symmetry codes: (i) *x*, *y*, *z*+1; (ii) −*x*+3/2, −*y*, *z*+1/2; (iii) *x*−1, *y*, *z*; (iv) *x*+1, *y*, *z*+1.