Crystal Structure of (*S*)-Piperazine-2-carboxylic acid *t*-butylamide/*N*-Tosyl-(*S*)-phenylalanine 1:2 Salt

Kayoko TANIGUCHI, Mikio YASUTAKE, and Takuji HIROSE[†]

Department of Applied Chemistry, Saitama University, Shimo-ohkubo 255, Sakura, Saitama, Saitama 338-8570, Japan

The crystal structure of the title salt was determined by X-ray diffraction. The compound crystallizes in a monoclinic space group, *C*2, with cell parameters *a* = 43.023(3) Å, *b* = 5.8504(5) Å, *c* = 16.6159(13) Å, β = 93.776(2)°, and *Z* = 4; the final residual factor, 0.0678, is for 7078 reflections.

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Piperazine-2-carboxylic acid *t*-butylamide, **1**, is one of the important key units of the HIV-1 protease inhibitor L-735,524.¹ Its effective resolution by *N*-tosyl-phenylalanine, **2**, using the diastereomeric salt formation method, was reported by Murakami *et al.*² We recently reported on the structures of both a less-soluble salt, (*S*)-**1**/(*S*)-**2**, and a more-soluble salt, (*R*)-**1**/(*S*)-**2**.³ Crystals of (*S*)-**1**/(*S*)-**2** and (*R*)-**1**/(*S*)-**2** were grown from 2-PrOH/H₂O (9:1) and EtOH solutions, respectively, and both contained the respective solvent molecule. However, when the less-soluble salt was recrystallized from EtOH, it was found that the stoichiometry became 1:2 by a ¹H NMR measurement. The interesting feature was investigated by an X-ray analysis of (*S*)-**1**/(*S*)-**2** (1:2) salt (Fig. 1).

The crystal data and the experimental details are summarized in Table 1. The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were located at geometrically calculated positions. The final parameters of non-hydrogen atoms are listed in Table 2, and the selected bond lengths and bond angles are given in Table 3. An ORTEP drawing of (*S*)-**1**/(*S*)-**2** (1:2) salt is illustrated in Fig. 2. The crystal packing of the (*S*)-**1**/(*S*)-**2** (1:2) salt is shown in Fig. 3 together with the (*R*)-**1**/(*S*)-**2** (1:1) salt.³

In the 1:1 crystal, 6 molecules of (*S*)-**2** form a box-like structure that contains 2 molecules of (*S*)-**1** and 2-PrOH, respectively (Fig. 3a). Only one nitrogen in the piperazine ring becomes an ammonium ion, and forms hydrogen bonds with two carboxyl groups. 2-Propanol is associated with the carboxyl group of (*S*)-**1** and the amide group of (*S*)-**2** through

the hydrogen bond.

On the other hand, in the 1:2 crystal, the (*S*)-**2** is bent and 2 molecules seem to strongly bind with (*S*)-**1** (Fig. 3b). The three-molecule unit aligns along the *c*-axis forming a layer,

Table 1 Crystal and experimental data

Formula	C ₄₁ H ₅₃ N ₅ O ₉ S ₂
Formula weight	824.00
Crystal color	colorless
Crystal description	needle
Crystal size	0.50 × 0.07 × 0.05 mm ³
Crystal system	monoclinic
Space group	<i>C</i> 2 (#5)
	<i>a</i> = 43.023(3) Å
	<i>b</i> = 5.8504(5) Å
	<i>c</i> = 16.6159(13) Å
	β = 93.776(2)°
<i>Z</i>	4
<i>V</i>	4173.2(6) Å ³
<i>T</i>	153(2) K
<i>D</i> _{calc}	1.312 Mg/m ³
μ (Mo <i>K</i> α)	0.188 mm ⁻¹
Radiation(Mo <i>K</i> α)	0.71069 Å
<i>F</i> (0 0 0)	1752
θ range for data collection	0.95 to 27.50°
Reflections collected	7078
Completeness	99.9%
Refinement method	full-matrix least-squares on <i>F</i> ²
No. of parameters	567
Goodness-of-fit on <i>F</i> ²	1.096
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0678, <i>wR</i> ₂ = 0.1592
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0881, <i>wR</i> ₂ = 0.1894
($\Delta\rho$) _{max}	0.503 e Å ⁻³
($\Delta\rho$) _{min}	-0.479 e Å ⁻³
Measurement	Bruker Smart Apex CCD diffractometer
Program system	STAIN
Direct methods	Sir97 ⁵
Refinement	SHELXL97 ⁷

CCDC 285871 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Fig. 1 Chemical structure of (*S*)-piperazine-2-carboxylic acid *t*-butylamide ((*S*)-**1**)/*N*-Tosyl-(*S*)-phenylalanine ((*S*)-**2**) 1:2 salt.

[†] To whom correspondence should be addressed.
E-mail: hirose@apc.saitama-u.ac.jp

Table 2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the non-hydrogen atoms

Atom	x	y	z	U_{eq}
C(1)	6681(1)	10444(7)	2238(2)	19(1)
C(2)	6532(1)	8817(7)	2832(2)	17(1)
O(1)	6580(1)	6725(5)	2736(2)	26(1)
O(2)	6388(1)	9651(6)	3389(2)	26(1)
N(1)	6478(1)	12405(7)	2040(2)	21(1)
S(1)	6215(1)	12265(2)	1309(1)	25(1)
O(3)	6104(1)	9962(6)	1259(2)	34(1)
O(4)	6002(1)	14084(7)	1427(2)	36(1)
C(3)	6399(1)	12873(9)	413(3)	27(1)
C(4)	6387(1)	11305(9)	-213(3)	29(1)
C(5)	6521(1)	11865(10)	-921(3)	36(1)
C(6)	6661(1)	13954(10)	-1024(3)	36(1)
C(7)	6676(1)	15506(9)	-377(3)	38(1)
C(8)	6541(1)	14974(9)	328(3)	36(1)
C(9)	6792(1)	14588(13)	-1816(3)	50(2)
C(10)	6990(1)	11236(8)	2634(3)	24(1)
C(11)	7188(1)	12706(8)	2112(2)	22(1)
C(12)	7276(1)	11947(10)	1372(3)	33(1)
C(13)	7467(1)	13296(11)	919(3)	46(2)
C(14)	7575(1)	15380(10)	1222(3)	39(1)
C(15)	7480(1)	16145(10)	1950(3)	39(1)
C(16)	7287(1)	14842(9)	2392(3)	30(1)
C(17)	6294(1)	4513(8)	4592(2)	20(1)
N(2)	6258(1)	4138(6)	3706(2)	17(1)
C(18)	5923(1)	4068(8)	3447(2)	23(1)
C(19)	5781(1)	2033(9)	3828(2)	24(1)
N(3)	5843(1)	1986(7)	4715(2)	22(1)
C(20)	6174(1)	2379(8)	4988(2)	21(1)
C(21)	6637(1)	4979(8)	4835(2)	21(1)
O(5)	6841(1)	4052(6)	4476(2)	31(1)
N(4)	6684(1)	6465(7)	5444(2)	21(1)
C(22)	6988(1)	7331(9)	5769(2)	25(1)
C(23)	7182(1)	5362(9)	6153(3)	34(1)
C(24)	6920(1)	9115(10)	6405(3)	37(1)
C(25)	7158(1)	8443(10)	5093(3)	36(1)
C(26)	5465(1)	8264(7)	6250(2)	20(1)
C(27)	5554(1)	6712(7)	5554(2)	18(1)
O(6)	5666(1)	7609(5)	4961(2)	24(1)
O(7)	5496(1)	4633(6)	5645(2)	27(1)
N(5)	5692(1)	10109(6)	6415(2)	21(1)
S(2)	6001(1)	9581(2)	6982(1)	23(1)
O(8)	6163(1)	11714(6)	7075(2)	35(1)
O(9)	6153(1)	7664(6)	6649(2)	31(1)
C(28)	5866(1)	8740(9)	7919(3)	25(1)
C(29)	5680(1)	10226(9)	8313(3)	30(1)
C(30)	5558(1)	9581(10)	9030(3)	36(1)
C(31)	5628(1)	7453(10)	9372(3)	31(1)
C(32)	5818(1)	5988(9)	8964(3)	33(1)
C(33)	5939(1)	6609(9)	8243(3)	29(1)
C(34)	5499(1)	6741(11)	10151(3)	45(1)
C(35)	5140(1)	9278(8)	6060(2)	24(1)
C(36)	4979(1)	10051(8)	6783(2)	22(1)
C(37)	4779(1)	8574(9)	7144(3)	30(1)
C(38)	4625(1)	9218(10)	7826(3)	36(1)
C(39)	4680(1)	11322(11)	8154(3)	42(1)
C(40)	4883(1)	12822(10)	7826(3)	38(1)
C(41)	5032(1)	12190(9)	7134(2)	29(1)

$$U_{\text{eq}} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* (\mathbf{a}_i \cdot \mathbf{a}_j).$$

Fig. 2 ORTEP drawing of (S)-1/(S)-2 (1:2) salt (50% probability).

which arranges in tilted stacks along the *a*-axis. Two carboxyl groups play the main role of the hydrogen network by forming salts with both nitrogen atoms of piperazine (O1...N2: 2.662(4) Å, O2...N2: 2.742(4) Å, O6...N3: 2.711(4) Å, O7...N3: 2.705(4) Å) and bonding with the sulfonamide nitrogen (O1...N1: 2.802(4) Å, O7...N5: 3.034(4) Å) (Supplementary data).

Table 3 Selected bond lengths (Å) and angles (°) for (S)-1/(S)-2 (1:2) salt

Atoms	Length	Atoms	Length
C(1)-N(1)	1.464(5)	C(1)-C(10)	1.517(6)
C(1)-C(2)	1.539(5)	N(1)-S(1)	1.607(3)
S(1)-C(3)	1.768(5)	C(10)-C(11)	1.522(6)
C(17)-N(2)	1.487(5)	C(17)-C(20)	1.519(6)
C(17)-C(21)	1.528(6)	N(3)-C(20)	1.481(5)
C(21)-N(4)	1.339(5)	C(26)-N(5)	1.468(5)
C(26)-C(35)	1.532(6)	C(26)-C(27)	1.538(5)
N(5)-S(2)	1.610(4)	S(2)-C(28)	1.768(4)
C(35)-C(36)	1.496(5)		

Atoms	Angle	Atoms	Angle
N(1)-C(1)-C(10)	110.4(4)	N(1)-C(1)-C(2)	111.3(3)
C(10)-C(1)-C(2)	107.4(3)	C(1)-N(1)-S(1)	120.6(3)
O(4)-S(1)-O(3)	119.7(2)	N(1)-S(1)-C(3)	107.04(18)
C(11)-C(10)-C(1)	115.6(3)	N(2)-C(17)-C(20)	107.0(3)
N(2)-C(17)-C(21)	108.8(3)	C(18)-N(2)-C(17)	109.1(3)
C(19)-N(3)-C(20)	114.0(3)	N(3)-C(20)-C(17)	110.1(3)
N(4)-C(21)-C(17)	114.2(4)	C(21)-N(4)-C(22)	125.9(3)
N(5)-C(26)-C(35)	109.9(4)	N(5)-C(26)-C(27)	112.3(3)
C(35)-C(26)-C(27)	110.0(3)	C(26)-N(5)-S(2)	118.8(3)
N(5)-S(2)-C(28)	105.15(19)	C(36)-C(35)-C(26)	114.6(3)

Fig. 3 Crystal packing of (a) (S)-1/(S)-2-PrOH 1:1:1 salt and (b) (S)-1/(S)-2 1:2 salt.

Many of them extend along the *b*-axis direction, except for O1...N2 and O7...N3. The carboxamide nitrogen seems to weakly interact with the sulfonamide oxygen (N4...O9: 3.212(4) Å) in the *c*-axis direction. In the 1:2 crystal, such a close packing, caused by the hydrogen bonds, allows no solvent molecules in the structure. In other words, the size of a crystallization solvent molecule seems to play an important role in the structure and the stoichiometry of the salts from (S)-1 and (S)-2.

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