Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Alaninyltryptophan hydrate, glycyltryptophan dihydrate and tryptophylglycine hydrate

T. J. Emge *et al.*

Electronic paper
This paper is published electronically. It meets the data-validation criteria for publication in Acta Crystallographica Section C. The submission has been checked by a Section C Co-editor though the text in the 'Comments' section is the responsibility of the authors.

Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Alaninyltryptophan hydrate, glycyltryptophan dihydrate and tryptophylglycine hydrate

T. J. Emge,[a]* A. Agrawal,[a] J. P. Dalessio,[a] G. Dukovic,[a] J. A. Inghrim,[a] K. Janjua,[a] M. Macaluso,[a] L. L. Robertson,[a] T. J. Stiglic,[a] Y. Volovik[a] and M. M. Georgiadis[a,b]

[a]Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8087, USA, and [b]Waksman Institute, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8087, USA
Correspondence e-mail: emge@rutchem.rutgers.edu

Received 21 July 2000
Accepted 29 August 2000

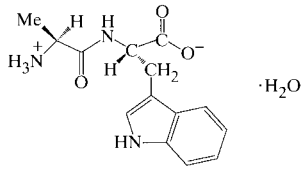
Data validation number: IUC0000233

The crystal structures of the title tryptophan-containing dipeptides, $C_{14}H_{17}N_3O_3\cdot H_2O$, (I), $C_{13}H_{15}N_3O_3\cdot 2H_2O$, (II), and $C_{13}H_{15}N_3O_3\cdot H_2O$, (III), respectively, contain at least one water molecule of solvation. As a result, the crystal packing of these compounds is composed of regions of water-mediated hydrogen bonding and tryptophan ring-to-ring stacking separated by the length of the molecule. The tryptophan rings stack in a continuous layer that, when viewed edge-on from the outermost part of the tryptophan ring, exhibits a herring-bone motif. However, owing to the lack of direct overlap of adjacent rings, no degree of π contact or long-range delocalization of ring systems is possible here. The overall molecular conformations of (I) and (III) contain a folding of one peptide over the other, such that a minimum in molecular volume occurs without any intramolecular hydrogen bonding. In these two dipeptides, extensive hydrogen bonding is observed to and from the single water molecule of solvation. In the crystal structure of (II), however, an extended molecule conformation complements a more extensive hydrogen-bonding scheme involving two water molecules of solvation per dipeptide.

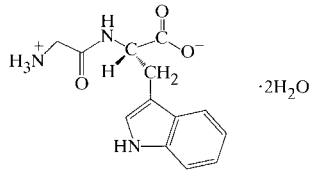
Comment

We have determined the crystal structures of three dipeptides containing tryptophan (Trp), namely alaninyltryptophan hydrate [Ala-Trp, (I)], glycyltryptophan dihydrate [Gly-Trp, (II)] and tryptophylglycine hydrate [Trp-Gly, (III)]. It is expected that the sequence and certain features of the solid-state peptide geometry will play a key role in the binding affinity and conformation of the peptide. Another important factor is the presence of significant hydrogen bonding due to the presence of water molecules in the immediate vicinity of the dipeptide. Noteworthy dipeptides (or higher peptides) containing Trp include Trp-Gly-Gly dihydrate (Subramanian & Sahayamary, 1989), Gly-Trp dihydrate (Pasternak, 1956) and Trp-Glu 7-methylguanosine-5′-phosphate trihydrate (Ishida *et al.*, 1991). The second of these, Gly-Trp, (II), needed to be redetermined [*e.g.* dated 1956 with $R(F) = 0.165$ and included no H-atom coordinates].

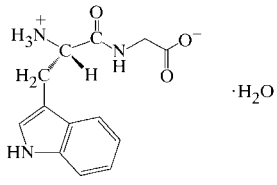
The role of hydrogen bonding of the dipeptide appears to be a generally important one for crystallization of the dipeptide hydrates (Allen *et al.*, 1983). In fact, the size and quality of the crystals formed after solvent evaporation generally follows the apparent strength and number of hydrogen bonds, namely (I) > (II) > (III). There are three short hydrogen-bond contacts in (I), and all are from the one water molecule of solvation to the dipeptide (*e.g.* no short water–water hydrogen-bond contacts).



(I)



(II)



(III)

The overall conformation of (I) is that of a hairpin that segregates the hydrogen-bond donors and acceptors on one side and the methyl and tryptophan groups on the other. The maximum atom–atom distance within the molecule is therefore short, at 9.0 Å. Analogous maxima for (II) and (III) are 11.6 and 8.6 Å, respectively. The hairpin or 'u' shape of (I) is also observed in (III), which contrasts the fully extended conformation of (II). The hairpin motif is also found in Trp-Gly-Gly (Subramanian & Sahayamary, 1989). These comformations are further described by the selected torsion angles about the respective dipeptide bonds (see Tables 1, 3 and 5). The unique hydrogen-bond contacts are comprised of the acceptor carboxylate, carbonyl and water O atoms and the donor protons from the water molecule and the primary and quaternary amines of the dipeptide bonds and the N termini. The two-dimensional networks of these sheets of hydrogen bonds extend throughout the crystallographic *ab, ab* and *ac* planes, respectively, for (I), (II) and (III). Connecting these layers of hydrogen-bond interactions, are layers of adjacent and parallel tryptophan rings. The tryptophan rings in these sheets, when viewed edge-on, compose a herring-bone motif rather than a direct ring-over-ring overlap. As a result, the interplanar separations are close [*e.g.* 3.3, 3.0 and 3.9 Å for (I), (II) and (III), respectively], but not overlapping. The non-overlapping herring-bone motif of tryptophan rings and adjacent sheets of hydrogen-bond interactions are obtained

for (II) and (III) also. This situation may be expected, although the tryptophan rings have been known to overlap directly with similar ring systems, such as that in tryptophanylglutamic acid 7-methylguanosine-5′-phosphate trihydrate (Ishida *et al.*, 1991). The unit-cell packing motif may thus be described as having alternating hydrogen-bond-containing (*e.g.* hydrophilic) regions and tryptophan ring (*e.g.* hydrophobic) regions. For (III), which has tetragonal symmetry, the hydrogen-bonding regions appear in both the *ac* and *bc* planes, the intersection of which contains rather large channels of hydrogen-bonding water molecules along the *c* axis.

Experimental

Crystallization of the dipeptides occurred upon solvent evaporation: 50 mg of dipeptide, 1 ml methanol and 1 ml water were combined in a 1-dram vial, placed with a loose-fitting cap on the shelf. The dipeptides were obtained from BAChem, the methanol was reagent grade (Fisher), and the water was distilled and deionized. Large colourless rods of (I) formed overnight after evaporation of either aqueous or 1:1 water–methanol solutions. The crystals of (II) also formed overnight from aqueous or 1:1 water–methanol solutions producing large colourless plates. The crystals of (III) formed only after very slow evaporation from the 1:1 water–methanol solution and produced only very thin irregularly shaped plates. Attempts to crystallize (I), (II) or (III) from non-aqueous solutions were not successful.

Compound (I)

Crystal data

$C_{14}H_{17}N_3O_3\cdot H_2O$
$M_r = 293.32$
Orthorhombic, $P2_12_12_1$
$a = 4.9475\ (5)$ Å
$b = 8.2059\ (12)$ Å
$c = 35.213\ (5)$ Å
$V = 1429.6\ (3)$ Å^3
$Z = 4$
$D_x = 1.363$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 26.1$–$28.8°$
$\mu = 0.841$ mm^{-1}
$T = 295\ (2)$ K
Rod, colourless
$0.35 \times 0.17 \times 0.15$ mm

Data collection

Nonius CAD-4 diffractometer
ω–θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.768$, $T_{max} = 0.881$
3190 measured reflections
2688 independent reflections
2538 reflections with $I > 2\sigma(I)$
$R_{int} = 0.0118$
$\theta_{max} = 70.00°$
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 10$
$l = -42 \rightarrow 42$
3 standard reflections
frequency: 60 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.026$
$wR(F^2) = 0.063$
$S = 1.004$
2688 reflections
267 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.025P)^2 + 0.315P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.14$ e Å^{-3}
$\Delta\rho_{min} = -0.10$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0259 (7)
Absolute structure: Flack (1983), 1067 Friedel pairs
Flack parameter = −0.02 (18)

Table 1
Selected geometric parameters (°) for (I).

H1N*A*—N1—C1—C2	−163 (1)	C2—N2—C4—C5	57.9 (2)
N1—C1—C2—N2	151.0 (1)	N2—C4—C5—O2	21.5 (2)
C1—C2—N2—C4	−176.8 (1)		

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1N*A*···O1*W*^{i}	0.97 (2)	1.77 (2)	2.720 (2)	166 (1)
O1*W*—H1W*B*···O3	0.95 (2)	1.79 (2)	2.737 (2)	171 (1)
O1*W*—H1W*A*···O2^{ii}	0.88 (2)	1.83 (2)	2.712 (2)	175 (1)
N1—H1N*B*···O2^{iii}	0.92 (2)	2.02 (2)	2.820 (2)	146 (1)
N1—H1N*C*···O3^{iv}	0.96 (2)	2.03 (2)	2.920 (2)	153 (1)
N2—H2N···O1^{v}	0.84 (2)	2.39 (2)	3.180 (2)	157 (1)

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

Compound (II)

Crystal data

$C_{13}H_{15}N_3O_3\cdot 2H_2O$
$M_r = 297.31$
Monoclinic, $P2_1$
$a = 5.8404\ (6)$ Å
$b = 8.2429\ (8)$ Å
$c = 14.8299\ (10)$ Å
$\beta = 96.178\ (8)°$
$V = 709.79\ (11)$ Å^3
$Z = 2$
$D_x = 1.391$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 35.4$–$42.8°$
$\mu = 0.907$ mm^{-1}
$T = 295\ (2)$ K
Plate, colourless
$0.60 \times 0.32 \times 0.02$ mm

Data collection

Nonius CAD-4 diffractometer
ω–θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.811$, $T_{max} = 0.982$
1583 measured reflections
1440 independent reflections
1404 reflections with $I > 2\sigma(I)$
$R_{int} = 0.015$
$\theta_{max} = 69.85°$
$h = 0 \rightarrow 7$
$k = 0 \rightarrow 10$
$l = -18 \rightarrow 17$
3 standard reflections
frequency: 3600 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.080$
$S = 1.002$
1440 reflections
263 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.0330P)^2 + 0.2950P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.17$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0227 (17)
Absolute structure: Flack (1983), no Friedel pairs
Flack parameter = 0.0 (3)

Table 3
Selected geometric parameters (°) for (II).

H1N*A*—N1—C1—C2	173 (2)	C2—N2—C3—C4	−76.1 (3)
N1—C1—C2—N2	−167.8 (3)	N2—C3—C4—O2	−26.9 (3)
C1—C2—N2—C3	−178.2 (2)	C3—N2—C2—O1	−0.1 (4)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1WA···O3	0.93 (5)	1.85 (4)	2.767 (3)	169 (3)
N1—H1NC···O1W^{i}	0.93 (5)	1.88 (6)	2.740 (4)	153 (4)
N1—H1NB···O2^{ii}	0.93 (4)	1.95 (4)	2.860 (3)	166 (3)
O2W—H2WA···O1	0.94 (7)	1.95 (6)	2.778 (4)	145 (4)
O2W—H2WB···O2^{ii}	1.07	1.97	3.034 (5)	179
N1—H1NA···O2W^{iii}	0.89 (5)	1.98 (6)	2.784 (4)	150 (4)
N2—H2N···O3^{iii}	0.90 (4)	2.00 (4)	2.884 (3)	164 (3)
O1W—H1WB···O2^{iv}	0.87 (7)	2.04 (6)	2.775 (4)	142 (4)

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

Compound (III)

Crystal data

$C_{13}H_{15}N_3O_3{\cdot}H_2O$
$M_r = 279.30$
Tetragonal, $P4_1$
$a = 16.128$ (2) Å
$c = 5.1950$ (10) Å
$V = 1351.3$ (4) Å^3
$Z = 4$
$D_x = 1.373$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 24.3$–$24.9°$
$\mu = 0.863$ mm^{-1}
$T = 295$ (2) K
Thin elongated plate,colourless
0.44 × 0.12 × 0.02 mm

Data collection

Nonius CAD-4 diffractometer
ω–θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.719$, $T_{max} = 0.996$
3174 measured reflections
1438 independent reflections
871 reflections with $I > 2\sigma(I)$
$R_{int} = 0.107$
$\theta_{max} = 70.03°$
$h = -13 \rightarrow 13$
$k = -10 \rightarrow 19$
$l = 0 \rightarrow 6$
3 standard reflections
frequency: 3600 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.061$
$wR(F^2) = 0.147$
$S = 1.005$
1434 reflections
250 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.04P)^2 + 1.00P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}
Extinction correction: *SHELXL*
Extinction coefficient: 0.0101 (13)
Absolute structure: Flack (1983), no Friedel pairs
Flack parameter = 0.6 (7)

Table 5
Selected geometric parameters (°) for (III).

H1NA—N1—C2—C1	167 (3)	C1—N3—C12—C13	60.7 (8)
N1—C2—C1—N3	154.7 (6)	N3—C12—C13—O2	30.5 (9)
C2—C1—N3—C12	178.1 (6)		

All H atoms were observed on difference Fourier maps. The positional and isotropic displacement parameters (U_{iso}) of the H atoms were refined, with C—H, N—H and O—H bond lengths in the ranges 0.92–1.02, 0.84–0.97 and 0.88–0.95 Å, respectively, for (I); 0.95–1.04, 0.89–0.93 and 0.87–0.94 Å, respectively, for (II); 0.91–1.01, 0.85–0.97 and 0.95–0.97 Å, respectively, for (III); except for H2WB of (II), which had x, y, and z fixed to the values observed on the map (O—H of 1.07 Å), and U_{iso} fixed to 0.35 Å^2. For the refinement of (III), the bond distances of the H atoms were restrained to the refined values from (I) with estimated standard deviations of 0.04 Å. Extinction corrections were significant in all of the structure determinations, and the following reflections were omitted from the refinement of (III): 1 1 0, 2 2 0, 1 2 0. No other reflections were omitted in the refinements. For each of the structures here, the stereochemistry of each peptide was known (natural, *l*- or *S*-conformation). The absolute structure determinations were not necessary, although (III) showed an ambiguous Flack parameter of 0.6 (7). For (III), the calculated ranges of indicies h, k and l are ±19, ±19 and ±6, respectively, for $\theta < 70°$. Some reflections with abs(h) > abs(k) were not measured, since their $-khl$ equivalents were collected. The presence of many weak reflections, the asymmetrical shape of the sample (very thin and long plate) and the likelihood of anisotropic extinction (*e.g.*, the isotropic value in *SHELXL*97 was high) led to an R_{int} value (0.106) that is slightly poorer than usually acceptable (<0.100).

Table 6
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1WA···O1W^{i}	0.97 (4)	1.75 (4)	2.695 (8)	163 (3)
O1W—H1WB···O2	0.95 (4)	1.84 (5)	2.738 (7)	156 (3)
N1—H1NA···O3^{ii}	0.93 (4)	1.95 (4)	2.868 (6)	170 (4)
N2—H2N···O3^{iii}	0.86 (3)	2.14 (4)	2.961 (6)	160 (3)
N1—H1NB···O2^{iv}	0.97 (4)	2.27 (4)	2.892 (6)	121 (3)
N1—H1NC···O1W	0.93 (4)	2.30 (4)	3.048 (7)	137 (4)
N1—H1NA···O2^{ii}	0.93 (4)	2.31 (4)	2.973 (8)	128 (4)

Symmetry codes: (i) $y, -x, z-\frac{1}{4}$; (ii) $-y, x, z-\frac{3}{4}$; (iii) $y, 1-x, z-\frac{1}{4}$; (iv) $-y, x, \frac{1}{4}+z$.

For all compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997).

This research was supported by a grant from the Howard Hughes Medical Institute.

References

Allen, F. H., Kennard, O. & Taylor, R. (1983). *Acc. Chem. Res.* **16**, 146–153.
Enraf–Nonius (1994). *CAD*-4 *EXPRESS*. Enraf–Nonius, Delft, The Netherlands.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Harms, K. & Wocadlo, S. (1995). *XCAD*4. University of Marburg, Germany.
Ishida, T., Iyo H., Ueda, H., Doi, M., Inoue, M., Nishimura, S. & Kitamura, K. (1991). *J. Chem. Soc. Perkin Trans.* 1, p. 1847.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Pasternak, R. A. (1956). *Acta Cryst.* **9**, 341.
Sheldrick, G. M. (1997). *SHELXL*97 and *SHELXS*97. University of Göttingen, Germany.
Subramanian, E. & Sahayamary, J. J. (1989). *Int. J. Pept. Protein Res.* **34**, 134.