

## Crystal structure of DL-Tryptophan at 173K

Ch. B. Hübschle, M. Messerschmidt, and P. Luger\*

Institut für Chemie / Kristallographie, Freie Universität Berlin, Takustr. 6, 14195 Berlin, Germany

Received 8 May 2003, accepted 3 September 2003

Published online 15 March 2004

**Key words** crystal structure, tryptophan, amino acid.

**PACS** 61.10. Nz

The crystal structure of pure *DL*-tryptophan has been determined at 173 K, using large but thin plate formed crystals of  $C_{11}H_{12}N_2O_2$ , which were grown by cooling down a saturated solution of *DL*-tryptophan in isopropanole / formic acid. The crystals are monoclinic, space group  $P 2_1/c$ , with the unit cell constants:  $a = 18.899(2)$ ,  $b = 5.7445(6)$ ,  $c = 9.309(1)$  Å,  $\beta = 101.776(2)$ ,  $V = 989.4(4)$ ,  $D_{\text{calc}} = 1.371$ ,  $Z = 4$ ,  $F(000) = 432$ ,  $\lambda(\text{MoK}\alpha) = 0.71073$  Å,  $\mu = 0.096$  mm<sup>-1</sup>. The crystal structure was solved by direct methods and refined by full-matrix least squares to a final R-factor = 4.03 % with 3343 unique reflections of which 2104 were observed. The molecule is zwitterionic in the crystal with the protonated amino group and the carboxylate group in unusual conformations with respect to the indole ring system compared to other tryptophan derivatives. A *D*- and *L*- molecular pair forms a dimer by N – H ... O hydrogen bonds via a crystallographic inversion center. The dimers are linked by further N – H ... O hydrogen bonds to form a head to head bilayer arrangement of the molecules in the crystal lattice. Except for weak van der Waals contacts there is no relation between indole tails of neighboured bilayers.

© 2004 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

### 1 Introduction

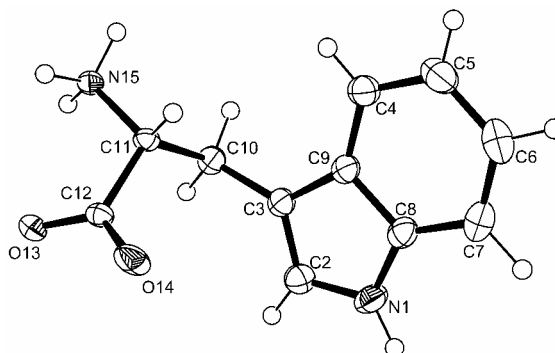
For most of the 20 genetically encoded amino acids the crystal structures are known at high precision, in several cases executed at low temperatures. One of the few exceptions where only moderate quality could be obtained is tryptophan, which is an essential  $\alpha$ -amino acid for humans. It is also a bionic precursor for the neurotransmitter serotonin (5-hydroxy-tryptamin (5-HT)), which is known as “happy hormone”. Due to the bad crystallisation properties the only non substituted tryptophan structure reported in the literature is that of *DL*-tryptophan [1] based on a room temperature data set with more than 70 % unobserved reflections, which did not allow, for example, a determination of hydrogen atoms. In this work we present a more precise investigation at a low temperature of 173 K, where all atoms including hydrogens were properly determined and refined, so that an improved model of this structure including more details of intermolecular hydrogen bonding interactions can be discussed.

### 2 Experiment

*DL*-tryptophan was dissolved in a warm mixture of 2-propanole and formic acid and the solution was cooled down slowly. A crystal was cut to the dimensions 0.5 x 0.4 x 0.15 mm. The X-ray data were collected on a Bruker AXS SMART 1K CCD diffractometer. Routine structure determination and refinement was performed using SHELXS97 and SHELXL97 [2]. In the course of the anisotropic refinement of the heavy atoms all

\* Corresponding author: e-mail: luger@chemie.fu-berlin.de

hydrogens were located from a difference synthesis and included for free refinement with isotropic displacement parameters in the final least squares cycles. Further experimental and refinement details are summarized in Table 1, final atomic parameters are in Table 2.



**Fig. 1** ORTEP [5] representation and labeling scheme for the molecular structure of DL-tryptophan.

**Table 1** Summary of Crystallographic Data.<sup>†</sup>

Formula	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>
Fw	204.23
Crystal shape	Plate
Crystal color	Colorless
Crystal size (mm)	0.5 x 0.4 x 0.15
Temperature (K)	173
Crystal system	Monoclinic
Space group	P 2 <sub>1</sub> /c (No. 14)
a (Å)	18.899(2)
b (Å)	5.7445(6)
c (Å)	9.309(1)
β (°)	101.776(2)
V (Å <sup>3</sup> )	989.4(4)
Z	4
Wavelength (Mo Kα) (Å)	0.71073
D <sub>calc</sub> (g/cm <sup>3</sup> )	1.371
μ (cm <sup>-1</sup> )	0.096
F(000)	432
Scan method	ω
2θ <sub>max</sub> (deg)	66.48
No. of reflections collected	11145
No. of independent reflections	3343
No. of reflections > 4 σ (F <sub>O</sub> )	2104
R <sub>int</sub> / R <sub>σ</sub>	0.096 / 0.0808
h <sub>min</sub> , h <sub>max</sub>	-28, 27
k <sub>min</sub> , k <sub>max</sub>	-8, 8
l <sub>min</sub> , l <sub>max</sub>	-14, 13
No. of variables, restraints	185, 0
Max shift/esd	0.000
R <sub>1</sub> /R <sub>w</sub>	0.0403 / 0.0913

<sup>†</sup> CCDC 210257 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccd.cam.ac.uk/counts/retrieving.html](http://www.ccd.cam.ac.uk/counts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)):

**Table 2** Atomic parameters of *DL*-tryptophan.

	x	y	z	$U_{eq}(\text{Å}^2)$
N1	0.31905(5)	0.2283(2)	0.3445(1)	0.0316(2)
C2	0.25068(6)	0.3039(2)	0.2846(1)	0.0288(2)
C3	0.23471(5)	0.4958(2)	0.3572(2)	0.0237(2)
C4	0.31523(6)	0.7188(2)	0.5746(2)	0.0301(3)
C5	0.38285(7)	0.7182(2)	0.6640(2)	0.0370(3)
C6	0.43346(7)	0.5465(2)	0.6507(2)	0.0389(3)
C7	0.41768(6)	0.3717(2)	0.5483(1)	0.0348(3)
C8	0.34929(6)	0.3729(2)	0.4579(1)	0.0266(2)
C9	0.29722(5)	0.5450(2)	0.4691(1)	0.0235(2)
C10	0.16596(6)	0.6306(2)	0.3255(1)	0.0235(2)
C11	0.11908(5)	0.5978(2)	0.4409(1)	0.0183(2)
C12	0.08497(5)	0.3569(2)	0.4331(1)	0.0189(2)
O13	0.12414(4)	0.1967(1)	0.4925(1)	0.0219(2)
O14	0.01971(4)	0.3381(1)	0.3680(1)	0.0325(2)
N15	0.06140(5)	0.7778(1)	0.4201(1)	0.0193(2)

### 3 Results and Discussion

The molecular structure is displayed in Fig. 1. together with the chosen atomic numbering scheme. A selection of bond lengths, angles and torsion angles is listed in Tables 3 and 4. Compared to the previous room temperature study [1] of this compound the eds's have been improved roughly by more than a factor of ten. The differences in bond lengths and angles between the present and the previous model amount in a few cases up to 0.07 Å and 6.3° respectively. The present bonding data is in agreement with the chemical expectations. Bond lengths and angles in the indole part of the molecule accomplish the geometrical predictions and need no further discussion. The molecule exists in its zwitterionic form as found for most of the amino acids in their crystalline state. In this form the  $C\alpha$  - N bond C11 - N15 is enlarged and the two C - O bonds are more alike than in a neutral COOH group where they differ normally by  $\approx 0.1$  Å.

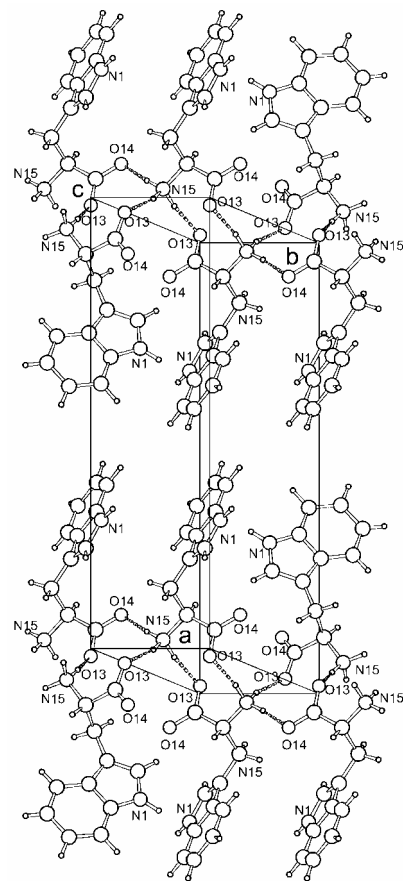
**Table 3** Bond lengths (Å).

N1	C2	1.370(2)
N1	C8	1.373(2)
C2	C3	1.359(2)
C3	C9	1.435(2)
C3	C10	1.490(1)
C4	C5	1.375(2)
C4	C9	1.393(2)
C5	C6	1.397(2)
C6	C7	1.374(2)
C7	C8	1.391(2)
C8	C9	1.414(1)
C10	C11	1.537(1)
C11	N15	1.486(1)
C11	C12	1.522(1)
C12	O14	1.238(1)
C12	O13	1.263(1)

Bakke and Mostad [1] have already pointed out that compared to other tryptophan derivatives the title compound has a unique orientation of the amino group with respect to the indole ring system. The torsion angle  $\chi^1$  (C3 - C10 - C11 - N15) is close to  $180^\circ$ , so that N15 is trans to C3 being otherwise close to a gauche arrangement ( $\chi^1 \approx \pm 60^\circ$ ). This causes C12 to be gauche to C3 indicated by  $\chi^{1,2} = -71.4(1)^\circ$  (C3 - C10 - C11 - C12) so that finally the carboxylate group is on the cis side of the C2 atom of the indole ring.

**Table 4** Selected bond angles and torsion angles of *DL*-tryptophan ( $^\circ$ ).

Angle			DL-tryptophan		
C3	C10	C11	113.71(8)		
N15	C11	C12	109.50(8)		
N15	C11	C10	109.61(8)		
C12	C11	C10	112.16(8)		
O13	C12	O14	125.95(9)		
O13	C12	C11	116.45(9)		
O14	C12	C11	117.60(8)		
Torsion angle					
DL-TRP (C11 is R)					
Nomenclature [3]					
C(2)	C(3)	C(10)	C(11)	107.9(1)	$\chi^{2,1}$
C(3)	C(10)	C(11)	N(15)	166.78(8)	$\chi^1$
C(3)	C(10)	C(11)	C(12)	-71.4(1)	$\chi^{1,2}$
N(15)	C(11)	C(12)	O(13)	21.7(1)	$\psi^2$
N(15)	C(11)	C(12)	O(14)	-158.0(1)	$\psi^1$
C(10)	C(11)	C(12)	C(13)	-100.3(1)	



**Fig. 2** Hydrogen bonding system and packing diagram of *DL*-tryptophan, made with SCHAKAL99 [4] . (symm: x,y,z; -x, 1/2 + y, 1/2 - z; -x, 1 - y, 1 - z; x, 1 + y, z; x, 1/2 + y, 1/2 - z; -x, 1 - y, 2 - z; dup : 1 + x , y, z;).

With hydrogen positions now available a complete hydrogen bonding system can be discussed (see Fig.2). The protonated amino group is donor of three hydrogen bonds in the crystal packing. The N15 – H15a ... O13 hydrogen bond is formed via the crystallographic inversion center so that the racemic compound forms a *DL*-dimer. The other two N – H ... O hydrogen bonds link these dimers via pure translation in b-direction (N15 - H15c ... O14) or via the crystallographic screw axis (N15 – H15b ... O13) forming a two dimensional network and stabilizing this way a head to head bilayer arrangement of the molecules next to  $x = 0, 1, \dots, n$ . The indole tails of neighboured layers approach close to  $x = 1/2$ . The indole nitrogen acts as a donor for a N – H ...  $\pi$ -hydrogen bond with a distance of 2.62 Å between the hydrogen and the center of the six-membered ring of the  $\pi$ -acceptor. This distance is quite short in comparison with the average of 2.71(1) Å given for such interactions in the literature [6]. This N – H ...  $\pi$  hydrogen bond is the only interaction between indole tails within one bilayer. There is no tail-to-tail interaction between different bilayers, except for van der Waals interactions with H ... C contacts > 3.3 Å. This could be the reason why the crystals are formed in such thin plates which can be cleaved very easily parallel to the largest crystal face.

**Table 5** Hydrogen bonding scheme. (Å, °).

donor	H-atom	acceptor	D – H	H ... A	D ... A	D – H ... A	symmetry
N 15	H 15A	O 13	0.96	1.87	2.81	171	-x, 1 - y, 1 - z
N 15	H 15B	O 13	0.97	1.88	2.83	165	-x, 1/2 + y, 1/2 - z
N 15	H 15C	O 14	0.99	1.72	2.71	175	x, 1 + y, z
N1	H1	$\pi$ (6 – ring)	0.91	2.62	3.35	137	x, 1/2 - y, z - 1/2

## References

- [1] Ø. Bakke and A. Mostad, Acta Chem. Scand. B. **34**, 559 (1980).
- [2] G. M. Sheldrick, SHELXS97 and SHELXL97. University of Göttingen, Germany (1997).
- [3] IUPAC-IUB Commission on Biochemical Nomenclature, J. Mol. Biol. **52**, 1, (1970).
- [4] E. Keller and J. -S. Pierrard, SCHAKAL99, University of Freiburg, Germany (1999).
- [5] M. N. Burnett and C. K. Johnson, ORTEPIII. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee USA (1996).
- [6] G. R. Desiraju and T. Steiner, The Weak Hydrogen Bond in Structural Chemistry and Biology. New York: Oxford University Press Inc. (1999).