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Boc-tyrosyl-D-alanyl-glycyl-*N*-methyl-phenylalanyl-*O*-methyl-methionine hydrate: a protected analog of metkephamid

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Key indicators

Single-crystal X-ray study
T = 153 K
Mean σ(C–C) = 0.005 Å
Disorder in solvent or counterion
R factor = 0.043
wR factor = 0.112
Data-to-parameter ratio = 10.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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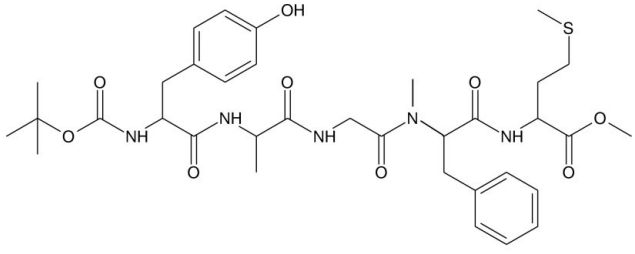
In this study, we report on the X-ray diffraction analysis of the pentapeptide, Boc-Tyr-D-Ala-Gly-(NMe-Phe)-(Met-O-Me), $C_{35}H_{49}N_5O_9S\cdot1.125H_2O$. This is a protected intermediate in the solution phase synthesis of metkephamid (LY127,623), Tyr-D-Ala-Gly-NMe-Phe-Met-NH2. The peptide crystallizes in the monoclinic space group *C*2 with two peptide molecules and three solvent (water) molecules in the asymmetric unit. The peptide has an extended conformation similar to other *Met*-enkephalins.

Comment

Theoretically, linear peptides can have many different backbone conformations. Early X-ray studies (1983–1987) on enkephalin and its analogs showed only two different backbone conformations: extended and single β-bend. No other conformations were observed until a double β-bend was reported in 1989 (for a review, see Deschamps *et al.*, 1996). Despite the small number of conformations observed in the solid state, most enkephalin analogs can adopt many conformations in solution. To constrain the peptide conformation a number of modifications have been investigated, including the substitution, deletion or addition of natural or artificial amino acids and the formation of highly constrained peptide ring systems. In this study, we report on the X-ray diffraction analysis of the pentapeptide, Boc-Tyr-D-Ala-Gly-(NMe-Phe)-(Met-O-Me), a protected intermediate in the solution phase synthesis of metkephamid (LY127,623). Metkephamide (Tyr-D-Ala-Gly-NMe-Phe-Met-NH2) is an analog of methionine-enkephalin that retains high affinity for the delta receptor, and has systemic analgesic activity (Frederickson *et al.*, 1981).



(I)

The title compound, (I), crystallizes with two peptide molecules and three water molecules in the asymmetric unit (Fig. 1). Additional disordered water molecules are probably present in the crystal, as evidenced by the diffuse residual electron density, and voids large enough to accommodate a water molecule were detected by *PLATON* (Spek, 2001). The two independent peptides molecules have an extended

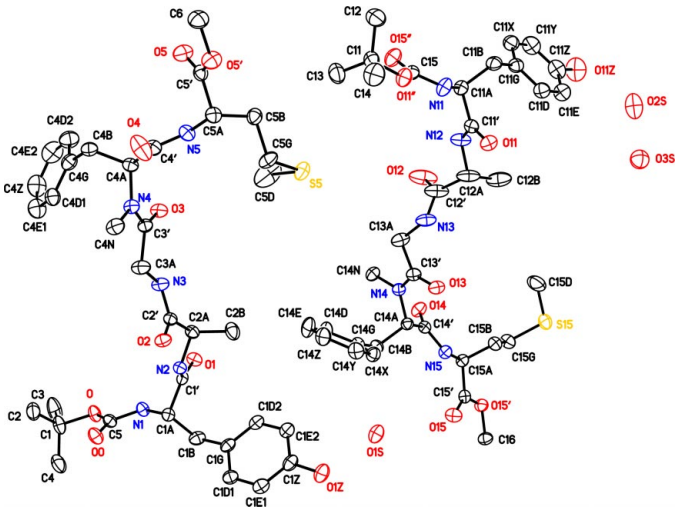


Figure 1
The structure of Boc-Tyr-D-Ala-Gly-NMe-Phe-Met-OMe showing the relationship of the two independent peptide molecules and the associated water molecules. Displacement ellipsoids are shown at the 30% probability level.

conformation, although even the main-chain atoms cannot be fully superimposed (Fig. 2). The extended conformation observed in this study is similar to that of other *Met*-enkephalins (Doi *et al.*, 1984; Griffin *et al.*, 1986; Doi *et al.*, 1987).

The peptide molecules form an extensive hydrogen-bonded network (Table 1). Pairs of adjacent peptide molecules are linked across the chains by six hydrogen bonds (Fig. 3). These pairs are then linked to adjacent pairs by two hydrogen bonds forming extended ribbons. This pattern of cross-chain hydrogen bonds is typical of enkaphalins with an extended conformation (Karle *et al.*, 1983; Griffin *et al.*, 1986; Doi *et al.*, 1987). Two of the solvent (*i.e.* water) molecules form hydrogen

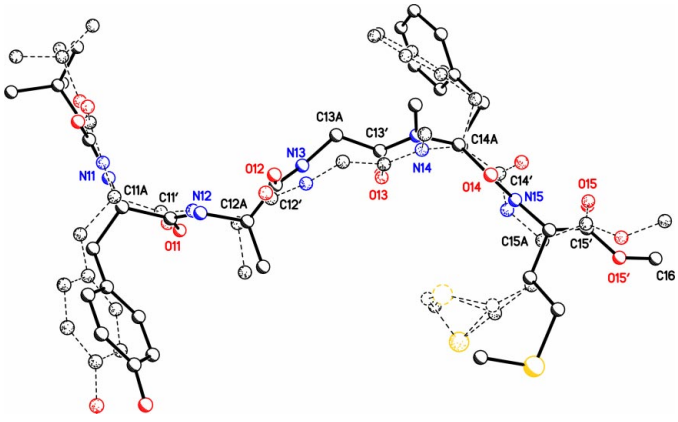


Figure 2
The conformation of Boc-Tyr-D-Ala-Gly-NMe-Phe-Met-OMe. The two independent peptide molecules are superimposed (alignment was based on the positions of the main-chain N and O atoms). Although the two independent molecules have similar conformations, even the main-chain atoms cannot be superimposed. Additional differences are present in the orientations of the side chains.

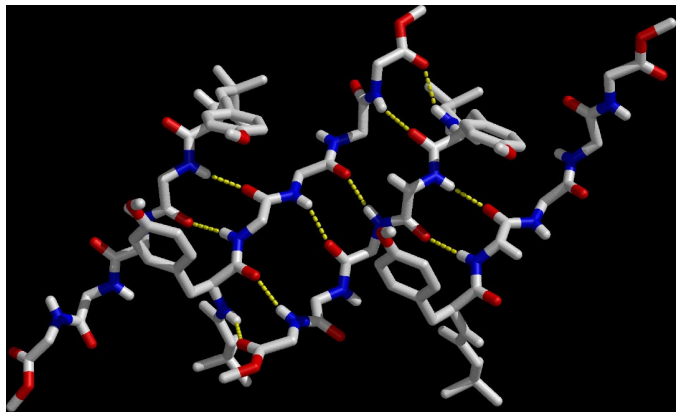


Figure 3
Inter-chain hydrogen bonding in Boc-Tyr-D-Ala-Gly-NMe-Phe-Met-OMe. The six hydrogen bonds between the pair of peptide molecules in the asymmetric unit and the two hydrogen bonds connecting adjacent pairs are shown as dashed lines. Solvent molecules and side chains not involved in hydrogen bonding have been omitted for clarity.

bonds between adjacent ribbons; the third water molecule (O3*S*) interacts only with other solvent molecules.

In this study, the X-ray diffraction data were collected using a Bruker SMART 6000 detector and a copper rotating anode. Prior to this, we collected X-ray diffraction data at the Cornell High Energy Synchrotron Source (CHESS). The structure determined from the synchrotron data is identical to that reported here. However, the synchrotron determined structure suffered from an incomplete dataset (due to the experimental set up) and unusually large sigmas for the measured intensities. Because of these problems the structure-solution for the synchrotron data was more difficult and the structure did not refine as well.

Experimental

The peptide, Boc-Tyr-D-Ala-Gly-NMe-Phe-Met-OMe, was supplied by Research Triangle Institute and was prepared using standard methods of peptide synthesis. Crystals were grown by vapor diffusion of petroleum ether into acetone.

Crystal data

$C_{35}H_{49}N_5O_9S\cdot1.125H_2O$
M_r = 735.87
Monoclinic, $C2$
a = 38.354 (1) Å
b = 11.000 (1) Å
c = 22.689 (1) Å
β = 123.15 (1)°
V = 8014.4 (8) Å^3
Z = 8
D_x = 1.220 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 928 reflections
θ = 5.5–124.6°
μ = 1.21 mm^{-1}
T = 153 (2) K
Prism, colorless
0.52 × 0.50 × 0.46 mm

Data collection

Bruker SMART 6000 CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
T_{min} = 0.559, T_{max} = 0.573
17149 measured reflections
10567 independent reflections
8802 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 65.1°
h = −42 → 44
k = −12 → 12
l = −26 → 25

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0576P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.043$	$(\Delta/\sigma)_{max} = 0.056$
$wR(F^2) = 0.112$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
$S = 1.01$	$\Delta\rho_{min} = -0.23$ e Å^{-3}
10567 reflections	Extinction correction: *SHELXL*97
966 parameters	Extinction coefficient: 0.000290 (16)
H atoms treated by a mixture of independent and constrained refinement	Absolute structure: Flack (1983)
	Flack parameter = 0.00 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···O15	0.86	2.29	3.036 (3)	145
O1*Z*—H1*ZA*···O1S	0.82	1.89	2.708 (3)	179
N2—H2*D*···O2^{i}	0.86	2.11	2.960 (3)	169
N3—H3*D*···O13	0.86	2.26	3.029 (3)	149
N5—H5*A*···O11	0.86	2.07	2.865 (3)	153
N11—H11*A*···O5	0.86	2.26	3.017 (3)	146
O11*Z*—H11*G*···O2*S*^{ii}	0.82	1.93	2.745 (5)	175
N12—H12*D*···O12^{iii}	0.86	2.10	2.956 (4)	171
N13—H13*D*···O3	0.86	2.05	2.902 (3)	169
N15—H15*A*···O1	0.86	2.00	2.828 (3)	161
O1*S*—H1*SA*···O2^{iv}	0.85 (4)	2.02 (4)	2.842 (3)	164 (3)
O1*S*—H1*SB*···O0^{ii}	0.86 (3)	2.00 (3)	2.827 (3)	160 (4)
O2*S*—H2*SA*···O15"	0.89 (2)	1.93 (2)	2.821 (3)	175 (4)
O2*S*—H2*SB*···O3*S*^{iii}	0.87 (2)	1.76 (3)	2.521 (14)	144 (4)
O2*S*—H2*SB*···O3*S*	0.87 (2)	2.01 (3)	2.768 (14)	144 (3)

Symmetry codes: (i) $-x, y, 1-z$; (ii) $x, 1+y, z$; (iii) $-x, y, -z$; (iv) $-x, 1+y, 1-z$.

The displacement parameters of the terminal methyl group on the disordered methionine side chain were constrained using the ISOR instruction (isotropic approximation) in *SHELXTL* (Sheldrick, 1997*b*). Difference peaks for the H atoms on two of the water molecules were located. The positions of these H atoms were refined with the O—H and H···H distances restrained to reasonable values.

Data collection: *SMART* (Bruker, 1999); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*a*); molecular graphics: *SHELXTL* (Sheldrick, 1997*b*); software used to prepare material for publication: *SHELXL*97.

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