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КРАТКИЕ СООБЩЕНИЯ

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CRYSTAL STRUCTURE OF THE CO-CRYSTAL ALA-VAL·ALA·H_2O: A LAYERED INCLUSION COMPOUND

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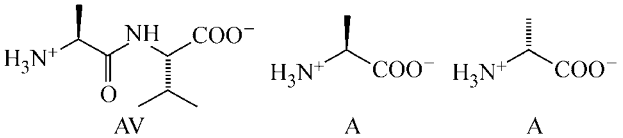
A co-crystal of L-alanyl-L-valine (AV) and L-alanine (A), AV·A·(H_2O), has been prepared and characterized by single crystal XRD analysis. Crystal data: $C_{11}H_{25}N_3O_6$; M = 295.3; orthorhombic, space group $P2(1)2(1)2(1)$; a = 16.4773(17), b = 18.3932(19), c = 5.0398(5) Å, V = 1527.4(3) Å^3, Z = 4; d_{calc} = 1.284 g/cm^3. Experimental parameters: T = 100 K; diffractometer, radiation: Kappa APEX II, graphite-monochromatized MoK_α; R_1 = 0.046, wR^2 = 0.120 for 4639 unique reflections and 214 refinement parameters. The L-alanyl-L-valine dipeptide molecules assemble to form a parallel β-sheet through hydrogen bonds, while the L-alanine molecules fill the large channels located in the interlayer space. AV·A·(H_2O) is the first layered structure based on a representative of hydrophobic dipeptides that form hexagonal tubular structures in the solid state, as well as the first inclusion compound of AV with a chiral guest.

Keywords: L-alanyl-L-valine, L-alanine, crystal structure, co-crystal, dipeptide, amino acid, β-sheet, layered structure, clathrate, channel.

Recently there has been growing interest in the solid-state structure of hydrophobic dipeptides [1—3]. These biologically relevant molecules have high potential for creating co-crystals with molecules of another kind, through co-crystallization and/or an inclusion process. The resulting materials may become useful in various applications, such as chiral separations and storage of drugs, as the dipeptides are water-soluble, non-toxic and degradable components.

Two characteristic types of H-bonded assemblies of dipeptide molecules observed in the crystals are of special interest. Tubular structures (AV and others) possess cavity space in the form of channels and produce co-crystals through the inclusion of guest molecules in the channels. Layered structures (LL and others) possess interlayer cavity space that is available for the second (guest) component.



AV (LL-isomer) A (L-isomer) A (D-isomer)

The AV dipeptide (L-alanyl-L-alanine, see Scheme) utilized in this work forms a microporous hexagonal structure with a tubular H-bonded assembly of the molecules surrounding a hydrophobic channel, the widest channel in the series of similar materials [3]. Nevertheless, the maximum size of the guest molecule that can be included in the channel is relatively small, scored by *iso*-propanol, which induces significant distortions of the structure to fit the cavity space [4]. The channel structure

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is the only crystal structure reported for this dipeptide which appears to be very stable in spite of the low density of the guest-free crystal [5]. The channel form could well crystallize with empty channels in the presence of larger guest species. In the course of our investigations we became interested in the ability of the AV dipeptide to co-crystallize with medium-sized molecules, possibly with the formation of new, previously unknown for AV, crystal structure types. Attempts to co-crystallize AV with L- and D-isomers of alanine were undertaken in the present study.

Experimental. Preparations. L-alanyl-L-valine (Chem-Impex) and D- and L-alanines (Aldrich) were obtained commercially and used without further purification. Co-crystals of L-alanyl-L-valine and L-alanine were obtained by evaporation of a 1:1 aqueous solution of the components. The sample contained three types of colorless crystals: long thin needles of hexagonal AV (channel structure [3, 5]), plates of A [6] and prisms of the title AV·A·(H_2O). The AV·A·(H_2O) co-crystals were present in the smallest quantity.

PXRD. Powder XRD patterns were recorded at room temperature on a Bruker AXS D8 Advance X-ray diffractometer using CuK_α radiation. Samples were scanned over the range $5° < 2\theta < 35°$.

Crystallography. Screening of single crystals was accomplished on a Bruker-Nonius Kappa Apex II diffractometer using graphite monochromatized MoK_α radiation (λ = 0.71073 Å). Three sets of frames were measured to determine the unit cell of a crystal in order to assign the crystal to either the previously known (AV or A) or a new structure.

A single 0.55 × 0.20 × 0.18 mm colorless prism of the title compound suitable for single crystal XRD measurements was mounted on a formvar foil and cooled down to the experimental temperature of 100 K. Intensity data were collected and corrected for Lorentz and polarization effects with a multi-scan absorption correction (SADABS). The crystal structure was solved by direct methods and refined by full-matrix least-squares routine using the SHELXTL program suite. Except for minor components of disordered atoms, all non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were calculated geometrically and were riding on their respective carbon atoms. Crystal data: $C_{11}H_{25}N_3O_6$; M = 295.3; orthorhombic, space group $P2(1)2(1)2(1)$; a = 16.4773(17), b = 18.3932(19), c = 5.0398(5) Å, V = 1527.4(3) Å^3, Z = 4; d_{calc} = 1.284 g/cm^3. Experimental parameters: T = 100 K; 27682 reflections measured ($2.7 < 2\theta < 30.5°$); 4639 unique reflections (R_{int} = 0.030); GOOF on F^2 = 1.045, R_1 = 0.046, wR^2 = 0.120 for 4639 utilized reflections and 214 refinement parameters; residual extrema: highest peak 0.26 e/Å^3, deepest hole –0.39 e/Å^3. A CIF file containing complete information on the studied structure was deposited with the CCDC, deposition number 644509, and is freely available upon request from the web site www.ccdc.cam.ac.uk/data_request/cif.

Results and discussion. Stoichiometry, nature and stability of the title compound. A crystal of one novel compound was isolated and studied in this work. The stoichiometry of the compound is AV·A·(H_2O) and by its nature it is a co-crystal of two chiral molecules, L-Ala-L-Val and L-alanine, with an additional molecule of solvent water. Here the compound is described as an inclusion compound of AV as host with A as guest because of the similarity of its crystal structure with typical layered inclusions of some other dipeptides as elaborated in the next section.

Crystals of AV·A·(H_2O) were obtained by evaporation of a 1:1 aqueous mixture of AV and A. The sample contained three types of colorless crystals: long thin needles, plates, and prisms. The three crystal forms of the sample were easily distinguishable. The needles and plates were identified as the previously characterized hexagonal channel-type structure of AV [3—5] and pure layered form of A [6], respectively, while the prisms were determined to belong to the title compound. The AV·A·(H_2O) co-crystals were present in only a very small quantity in the sample. Other crystallizations conducted in similar conditions yielded only mixtures of AV and A. The same mixture was obtained after prolonged equilibration (stirring at room temperature for 1 day) of the crystalline mass under liquor solution (as attested by powder XRD). From these observations we conclude that the title AV·A·(H_2O) compound formed in the ternary system AV — A — H_2O as a metastable product.

Our attempts to prepare co-crystals from AV and D-alanine (D—A) and from AV and D/L-alanine (D/L—A) were unsuccessful. Screening of the samples with both single crystal and powder

XRD methods indicated only the presence of pure AV and A phases (racemic and optically pure A have a similar crystal structure [6]).

Crystal structure of AV·A·(H_2O). The compound AV·A·(H_2O) crystallizes in the orthorhombic space group *P*2(1)2(1)2(1) and contains a 1:1:1 ratio of AV, A and H_2O. Both the AV and A components of the co-crystal exist as zwitterions with terminal NH_3^+ and COO^- groups. The isopropyl side chain of AV was found to be disordered and was modeled over three positions as a 50:36:14 mixture. The labeling scheme of the asymmetric unit is shown in Figure, left.

The dipeptide molecules assemble to form a parallel β-sheet in the *bc*-plane (Figure, middle). Within the sheet, the AV molecules align in a head-to-tail fashion along the *b*-axis, forming chains through COO^-…NH_3^+ hydrogen bonds [N1…O2A* = 2.820(2) Å]. The chains then stack parallel along the *c*-axis and associate through weak N—H…O=C hydrogen bonds [N2…O1A = 3.176(2) Å], forming the two-dimensional sheet (Figure, middle). The water molecules are part of the sheet structure; they are situated between the dipeptide chains and form H-bonds to dipeptide molecules from chains above and below [O6…N1 = 2.822(2), O6A…O2 = 2.489(4) Å].

The β-sheets pack along the *a*-axis and are related by a 2_1 screw axis. The interlayer space is partially filled with hydrophobic side fragments of the AV molecules. Large channels formed in the residual interlayer space are occupied by the L-alanine molecules (Figure, right). Pairs of L-alanine molecules sit side-by-side on the same level in the channel, which runs along the c-axis. Each molecule is connected to the second molecule of the pair with two H-bonds (N3...O5A and O5...N3A = = 2.783(2) Å) and to two other L-alanine molecules on upper and lower levels (N3...O4B and O4...N3C = 2.791(2) Å). In addition, the L-alanine molecule forms H-bonds to dipeptide molecules of the channel wall (O4...N1A = 2.709(2) Å; N3...O3B = 2.713(2) Å; N3...O4B = 2.791(2) Å).

The AV·A·(H_2O) co-crystal is related to a series of inclusion compounds of the LA dipeptide (L-leucyl-L-alanine) with dimethyl, benzyl methyl and isobutyl methyl sulfoxides as guests [7, 2], arylglycyl-arylglycines with various guests [8—11], and LL (L-leucyl-L-leucine) with dimethyl sulfoxide [12] and alcohols [13, 14]. The dipeptide molecules of these inclusions form similar layered structures as AV in the title compound, with the guest molecules located in the void spaces between the layers. In one of those structures water molecules also take part in the construction of a β-sheet layer [8].

Conclusion. This paper reports the first layered structure of the AV dipeptide, where AV molecules assemble in a typical β-sheet layer. This fact demonstrates that dipeptides that usually form tubular microporous structures may form, in the presence of larger guest species, layered inclusion

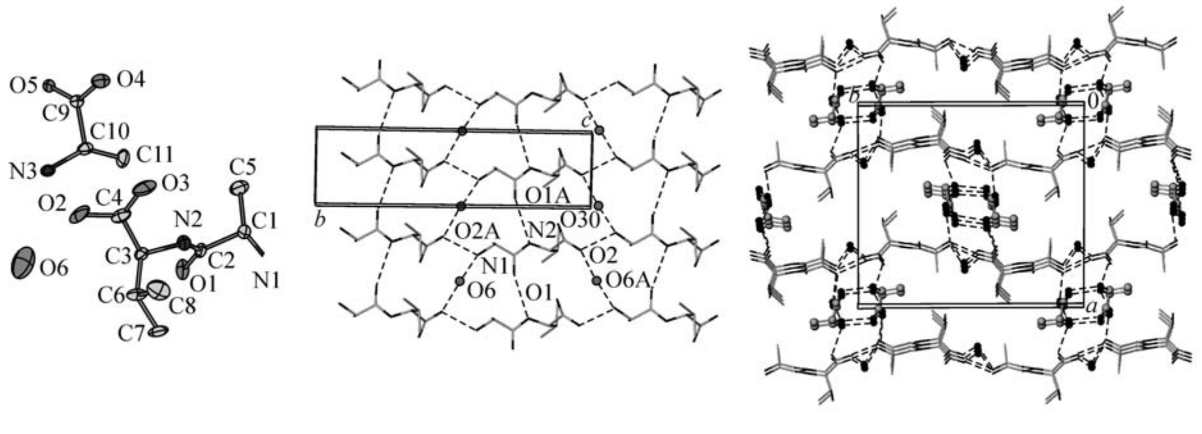

Figure. Left: The asymmetric unit of AV·A·(H_2O). Ellipsoids are shown at 50 % probability. H-atoms and minor components of disordered atoms have been omitted for clarity. Middle: The β-sheet formed in the *bc*-plane by H-bonding between AV molecules. Right: View of the packing of AV·A·(H_2O) in the *ab*-plane and the channels formed between adjacent β-sheets

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* Here and later in the text atom names ending with a letter designate atoms symmetrically related to the corresponding atom of the asymmetric unit.

structures and, therefore, may be considered for chiral separation and inclusion of practically important optically active species.

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