

The crystal structures of L-leucinium hydrogensquarate monohydrate and DL-leucinium hydrogensquarate

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The crystal structures of L-leucinium hydrogensquarate monohydrate (**1**) and DL-leucinium hydrogensquarate (**2**) are reported. Compound **1** crystallizes in the monoclinic space group $P2_1$ with two formula units in the asymmetric unit ($Z = 4$, $Z' = 2$) and exhibits *pseudo* inversion symmetry. The crystal structure of **1** features two crystallographically distinct stacked hydrogen-bonded β -chains of hydrogensquarate ions interconnected by hydrogen-bonded water molecules, surrounded by hydrogen-bonded L-leucinium ions, resulting in an intricate O-H \cdots O and N-H \cdots O hydrogen-bonded layer structure. Compound **2** crystallizes in the monoclinic space group $P2/n$ with $Z = 4$. Similar to **1**, the hydrogensquarate anions form β -chains in the crystal structure. Two symmetry-related β -chains are stacked and interconnected by hydrogen-bonded DL-leucinium ions, likewise affording an intricate O-H \cdots O and N-H \cdots O hydrogen-bonded sheet structure.

Keywords: leucine, amino acid, squaric acid, hydrogen bonding, crystal structure, *pseudo* symmetry.

INTRODUCTION

Squaric acid, $H_2C_4O_4$ (Scheme 1), is a remarkably strong diprotic organic acid. A pK_{a1} value of 0.51 ± 0.02 was obtained by conductometric determination [1] and $pK_{a1} = 0.55 \pm 0.15$ and $pK_{a2} = 3.480 \pm 0.023$ (at 25 °C) were determined by potentiometric titration [2]. Based on earlier studies, $pK_{a1} = 1.2\text{--}1.7$ was reported in a review article by Gilli *et al.* [3]. In any case, the strong acidity has been attributed to resonance stabilization of the corresponding anions, *i. e.* hydrogensquarate, $HC_4O_4^-$ (Scheme 1), and squarate, $C_4O_4^{2-}$ [4].

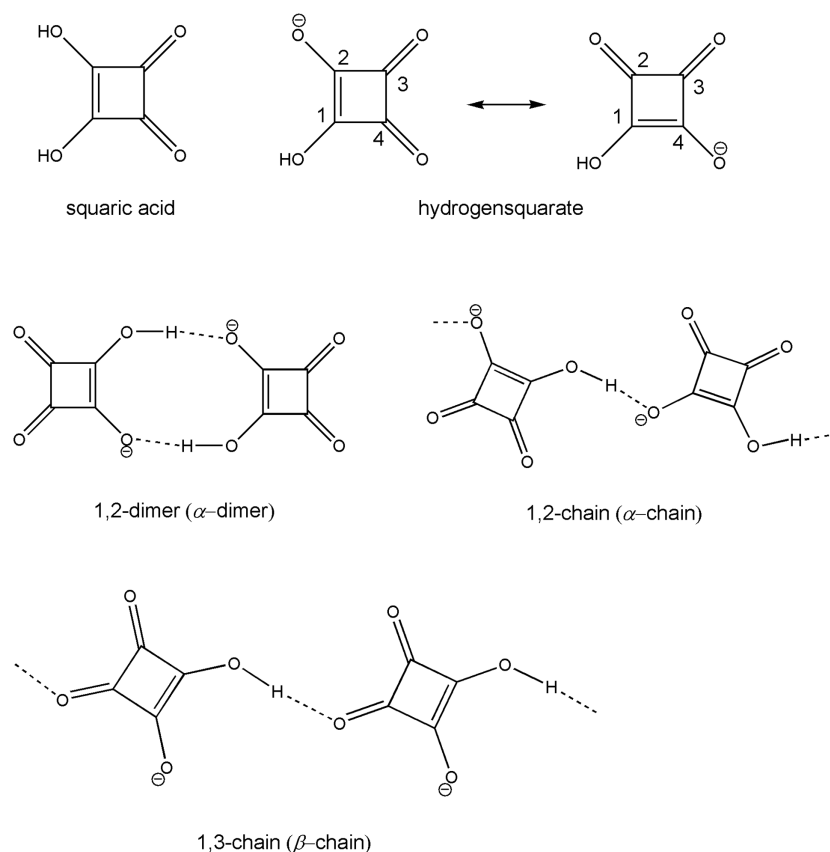
Since the 1990s, squaric acid anions have frequently been used as counterions for protonated organic bases in molecular salt crystals. A wide variety of such proton-transfer compounds can be found in the Cambridge Structural Database [5]. An early account of the crystal chemistry of squaric acid anions was given by Gilli *et al.* [3]. These authors ascribed the interest in these anions for crystal engineering to the following factors: first, the fact that donating and accepting hydrogen bonds

are confined to the molecular plane; second, the strength of the O-H \cdots O hydrogen bonds that hydrogensquarate ions can form to one another; third, the ability of squaric acid to readily transfer a proton to an aromatic base, which in turn forms a charge-assisted N-H \cdots O hydrogen bond to the anion. Three modes of association of hydrogensquarate ions *via* O-H \cdots O hydrogen bonds frequently encountered in the solid-state, *viz.* 1,2-dimers (α -dimers), 1,2-chains (α -chains) and 1,3-chains (β -chains) [3], are illustrated in Scheme 1.

Research into solid-state supramolecular chemistry of proton-transfer compounds of squaric acid and α -amino acids is driven by the general chemical and biological interest in α -amino acids and by the possibility to synthesize non-centrosymmetric crystals from enantiopure chiral α -amino acids. Non-centrosymmetry in the crystals is a requirement for desired non-linear optical properties of these materials. Kolev *et al.* [6–16] and others [17–19] have reported on the structures and properties of a variety of salts of squaric acid and α -amino acids and derivatives. Very recently, Yadav *et al.* reported a study on optical, piezoelectric, dielectric and mechanical properties of L-asparaginium hydrogen squarate hemihydrate crystals [20], which were first synthesized and structurally characterized by Kolev *et al.*

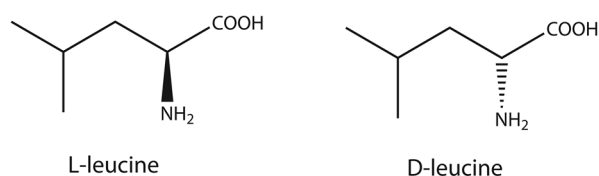
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Scheme 1. Chemical diagrams of squaric acid, hydrogensquarate resonance structures and some common hydrogen-bonded associations of hydrogensquarate [3].

[8]. Motivated by these results, we herein report the syntheses and crystal structures of L-leucinium hydrogensquarate monohydrate (**1**) and DL-leucinium hydrogensquarate (**2**). Chemical diagrams of the D- and L-form of the amino acid leucine are depicted in Scheme 2.



Scheme 2. Chemical diagrams of L-leucine and D-leucine.

EXPERIMENTAL SECTION

Preparation of **1** and **2**

224 mg (2 mmol) of squaric acid were dissolved in 30 mL of deionised water at 70 °C by continuous stirring for six hours. When the solution became

clear, 262 mg (2 mmol) of L-leucine or DL-leucine were added for the preparation of **1** and **2**, respectively. Stirring was continued for three hours without heating. Subsequently, the product was filtered off and purified by multifold recrystallization from deionised water.

Single-crystal X-ray analysis

The X-ray intensity data for **1** were collected on a Siemens P4 four-circle diffractometer with a scintillation detector, using graphite-monochromated Mo-K α radiation from a fine focus sealed X-ray tube. Unit cell parameters were determined by least-squares fit to the θ values of 15 automatically centred reflections ($7.5^\circ < \theta < 15.0^\circ$). The intensity data were collected in the ω scan mode. The data were corrected for Lorentz and polarisation effects. An absorption correction based on ψ scans was carried out [21]. The diffraction data for **2** were collected on a Bruker SMART X2S diffractometer, using Mo-K α radiation from a XOS X-beam microfocus X-ray source with a doubly curved silicon crystal monochromator. The data were processed with CrysAlisPro [22]. An absorption correction based

on multiple-scanned reflections [23] was carried out with ABSPACK in CrysAlisPro.

The crystal structures were solved by direct methods using SHELXS-97 [24] and refined by full-matrix least-squares refinement on F^2 using SHELXL-2018/3 [25]. The absolute structure of **1** was deduced from the known absolute configuration of the L-leucine starting material used for the synthesis. Anisotropic displacement parameters were introduced for all non-hydrogen atoms. Hydrogen atoms except for water molecules were placed at geometrically calculated positions and refined with the appropriate riding model. The positions of water hydrogen atoms were located *via* difference Fourier syntheses and subsequently refined with O-H distances restrained to target values of 0.82(2) Å. Crystal data and refinement details for **1** and **2** are given in Table 1. Representations of the crystal and molecular structures were drawn with DIAMOND [26]. Crystal data and refinement details are listed in Table 1.

CCDC 1433510 (**1**) and 1831823 (**2**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from the

Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/getstructures.

RESULTS AND DISCUSSION

Reaction of enantiopure L-leucine with an equimolar amount of squaric acid in aqueous solution afforded the crystalline monohydrate **1**, whereas treatment of racemic DL-leucine with squaric acid under the same reaction conditions yielded crystalline anhydrous **2**. Compound **1** crystallizes in the Sohncke space group $P2_1$. Figure 1 depicts the asymmetric unit of **1**, which comprises two L-leucinium ions, two hydrogensquarate ions and two water molecules, *i. e.* two formula units ($Z' = 2$). The two crystallographically unique hydrogensquarate ions are related by *pseudo* inversion symmetry. The ADDSYM routine in PLATON [27] calculates that the *pseudo* inversion symmetry expands to 94 % of the entire structure (*pseudo* space group $P2_1/n$). The *pseudo* symmetry encountered here is not a simple disorder, because the $h0l$: $h + l = 2n + 1$ reflections are not absent and the crystal structure

Table 1. Crystal data and refinement details for **1** and **2**

	1	2
Empirical formula	C ₁₀ H ₁₇ NO ₇	C ₁₀ H ₁₅ NO ₆
M_r	263.24	245.23
λ (Å)	0.71073	0.71073
Crystal size (mm ³)	0.23 × 0.13 × 0.11	0.54 × 0.30 × 0.25
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1/n$
T (K)	294(2)	300(2)
a (Å)	14.2880(17)	13.4301(19)
b (Å)	6.119(2)	6.0440(6)
c (Å)	15.0909(18)	14.9714(19)
β (°)	95.433(10)	92.189(12)
V (Å ³)	1313.5(6)	1214.3(3)
Z	4	4
ρ_{calc} (g cm ⁻³)	1.331	1.341
μ (mm ⁻¹)	0.114	0.112
$F(000)$	560	520
θ range (°)	2.063–24.991	2.000–25.053
Reflections collected / unique	3351 / 2977	6853 / 2141
R_{int}	0.0201	0.0394
Observed reflections [$I > 2\sigma(I)$]	2583	1714
Goodness-of-fit on F^2	1.024	1.112
Parameters / restraints	338 / 4	159 / 0
$R1$ [$I > 2\sigma(I)$]	0.0417	0.0712
$wR2$ (all data)	0.1160	0.1527
Residuals (eÅ ⁻³)	0.295 / -0.271	0.412 / -0.223

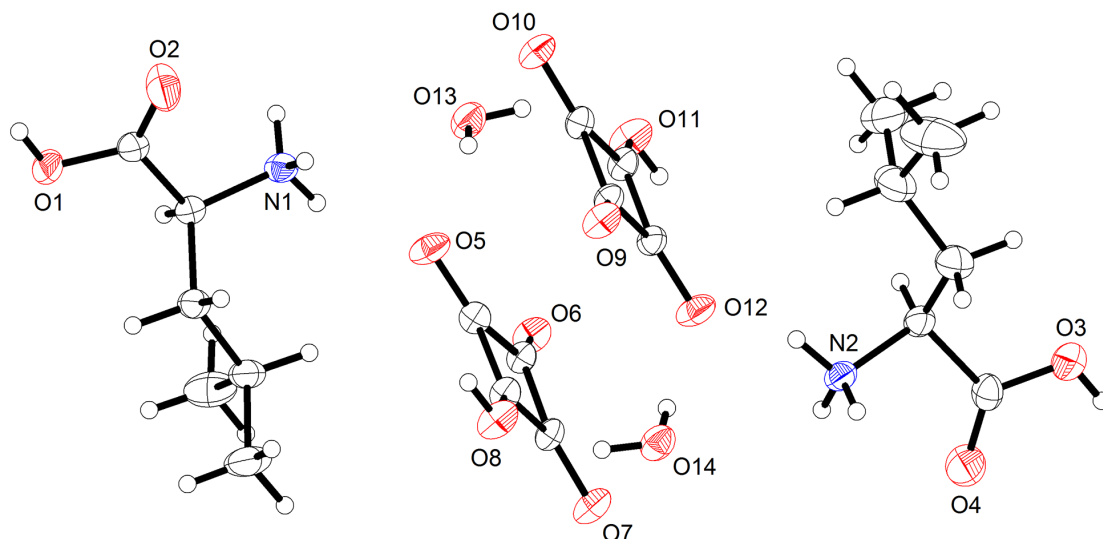


Fig. 1. Asymmetric unit of **1**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are represented by small spheres of arbitrary radii.

could be refined satisfactorily in the space group $P2_1$ with a non-disordered model. For some recent examples of *pseudo* symmetric crystal structures in the literature, see, for instance, references [28, 29]. In contrast to **1**, the asymmetric unit of **2** comprises only one formula unit (Fig. 2). Compound **2** crystallizes in the centrosymmetric space group $P2_1/n$.

In the crystal structure of **1**, the hydrogensquarate ions are joined by O-H \cdots O hydrogen bonds, resulting in two crystallographically distinct β -chains extending by translational symmetry in the b axis direction (Fig. 3). The O-H \cdots O distances within the β -chains are 2.571(4) and 2.57(4) Å, indicating strong hydrogen bonds. As aforementioned, the

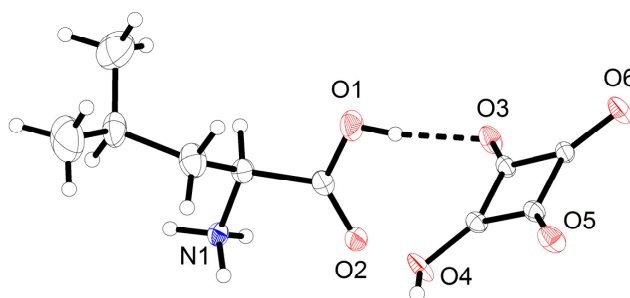


Fig. 2. Asymmetric unit of **2**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are represented by small spheres of arbitrary radii. The dashed line represents a hydrogen bond.

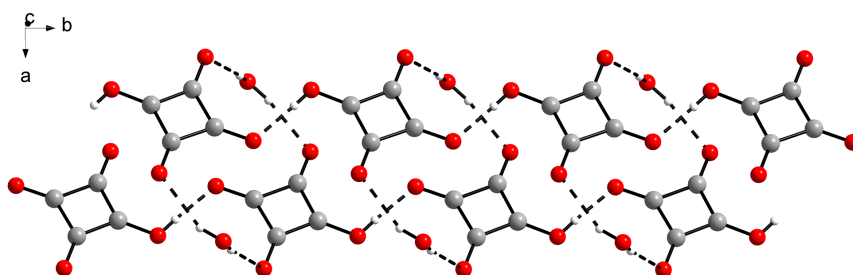


Fig. 3. View of the two crystallographically distinct oppositely extending stacked β -chains of hydrogensquarate ions in **1**, interconnected by water molecules, approximately along the c axis direction. Hydrogen bonds are represented by dashed lines.

hydrogensquarate ions in the distinct oppositely extending chains are related by *pseudo* inversion symmetry. The stacking distance between the chains is approximately 3.3 Å with respect to the mean planes. The water molecules interconnect the two β -chains via O-H \cdots O hydrogen bonds with an average hydrogen bond distance of 2.85 Å. The hydrogen-bonded strands of hydrogensquarate β -chains and water molecules are laterally linked by the L-leucinium ions via the carboxy and the protonated amino group. The carboxy groups form hydrogen bonds to hydrogensquarate oxygen atoms with distances of 2.610(4) and 2.618(4) Å. The average N-H \cdots O hydrogen bond distance is 2.89 Å. In the crystal, an intricate two-dimensional hydrogen bond network parallel to (10 $\bar{1}$) results (Fig. 4). A comprehensive listing of the hydrogen bond parameters in **1** can be found in the supporting crystallographic data.

As shown in Figure 5, the crystal structure of **2** likewise features hydrogen-bonded β -chains of hydrogensquarate ions extending by translational symmetry in the *b* axis direction. The O-H \cdots O

hydrogen bond distance is 2.592(3) Å. In contrast to **1**, however, the stacked β -chains in **2** do not extend oppositely but in the same direction. The two β -chains forming a stack are symmetry-related by a crystallographic twofold rotation axis, as also observed in the crystal structure of L-asparaginium hydrogen squarate hemihydrate [8, 20]. The stacking distance, *i. e.* the distance between the mean planes through the hydrogensquarate four-membered rings, is 3.21 Å and similar to that observed in **1**. It has been pointed out that β -chains of hydrogensquarate ions are strongly hydrophilic and therefore usually surrounded by water molecules in the crystal [3], as observed in **1**. Therefore, it is interesting to note that the structure of **2** is solvent-free, *i. e.* anhydrous, and the β -chains are exclusively surrounded by carboxy and protonated amino groups of the DL-leucinium ions, although **2** crystallized from water under the same conditions as **1**. The DL-leucinium ions link the stacks of β -chains into a two-dimensional hydrogen bond network parallel to (101) in the crystal (Fig. 6). The O-H \cdots O

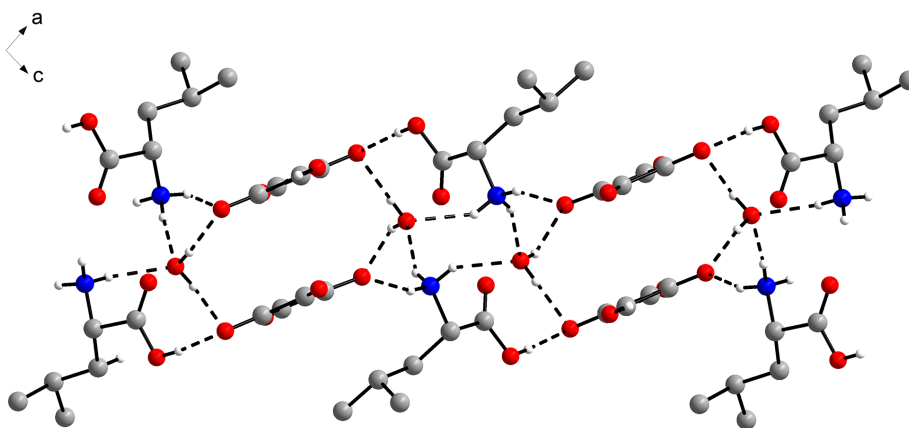


Fig. 4. O-H \cdots O and N-H \cdots O hydrogen-bonded sheet structure of L-leucinium ions, hydrogensquarate ions and water molecules in **1**, viewed along the *b* axis direction (along the β -chains). Hydrogen bonds are represented by dashed lines. Carbon-bound hydrogen atoms are omitted for clarity.

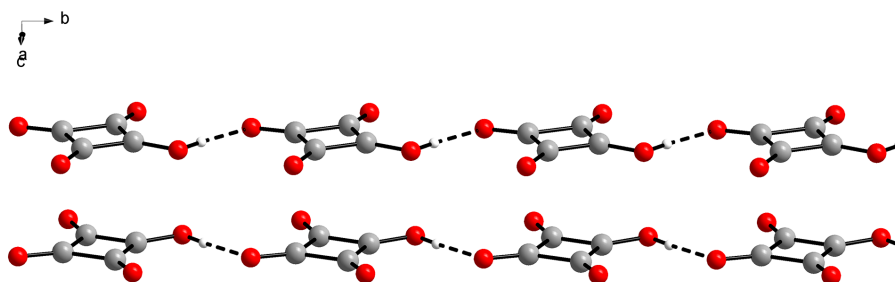


Fig. 5. View of two symmetry-related stacked β -chains of hydrogensquarate ions in **2**, extending in the same direction. Hydrogen bonds are represented by dashed lines.

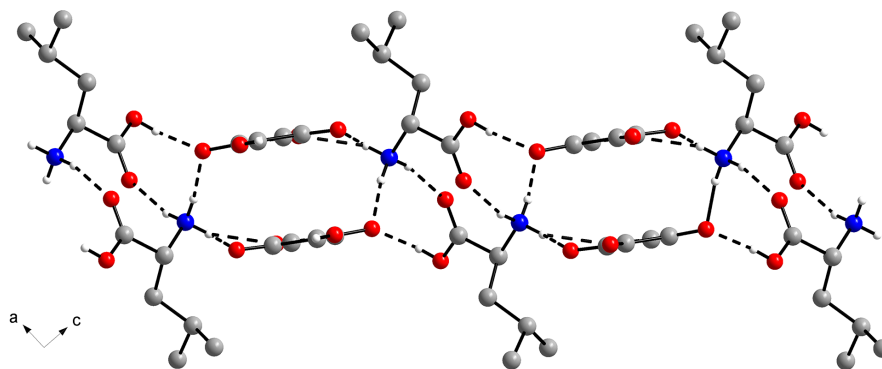


Fig. 6. O-H \cdots O and N-H \cdots O hydrogen-bonded sheet structure of DL-leucinium ions, hydrogensquarate ions in **2**, viewed along the *b* axis direction (along the β -chains). Hydrogen bonds are represented by dashed lines. Carbon-bound hydrogen atoms are omitted for clarity.

hydrogen bond distance involving the carboxy group is 2.592(3) Å. The protonated amino group forms a hydrogen bond to a carboxy oxygen atom of a neighbouring molecule [N-H \cdots O: 2.840(3) Å] and another to a hydrogensquarate oxygen atom [N-H \cdots O: 2.882(3) Å] and a donating bifurcated hydrogen bond to two hydrogensquarate oxygen atoms with an average N-H \cdots O hydrogen bond distance of 2.96 Å. In contrast to **1**, there is structural evidence for a weak hydrogen bond between the α -CH group of the leucinium ion and a hydrogensquarate oxygen atom [C-H \cdots O: 3.546(4), \angle CHO: 157.5°]. A comprehensive listing of the hydrogen bond parameters in **2** can be found in the supporting crystallographic data.

A survey of the Cambridge Structural Database [5] (CSD; version 5.39 with February 2018 updates) yielded a number of structurally characterized salts consisting of protonated α -amino acids and hydrogensquarate counterions. Similar to **2**, DL-serinium hydrogensquarate (CSD refcode: BUTBOJ) crystallizes solvent-free from a methanol/water mixture [16], but, in contrast to **2**, the hydrogensquarate ions form α -chains in the crystal. Topologically, the hydrogensquarate ions also form α -chains in the solvent-free structure of L-serinium hydrogensquarate (CSD refcode: PAZCUO) [8], but the flat hydrogensquarate ions are twisted to one another. α -Chains are also found in the monohydrate structure of the hydrogensquarate of (*R*)-1-phenylglycine (CSD refcode: TEHYUA) [7], a non-natural α -amino acid. The aforementioned L-asparaginium hydrogensquarate hemihydrate crystallizes from aqueous solution (CSD refcodes: NUIFUY and NUYFUI01) [8, 20] and features β -chains of hydrogensquarate ions in the crystal, similar to those in **2** but also surrounded by water molecules. β -Chains are also encountered in L-alaninium amide hydrogensquar-

ate monohydrate (CSD refcode: PAZFUS) [11] and L-prolinamidium hydrogensquarate (CSD refcode: TECMUK) [12]. The crystal structures of solvent-free L-argininium hydrogensquarate (CSD refcode: TIDCAK) [6] and L-argininamidium bis(hydrogensquarate) (CSD refcode: WEJCEU) [13] and show α -dimers of the hydrogensquarate ions. In the crystal structure of histidinium hydrogensquarate (CSD refcode: TIWXAY) [17], L-lysinium hydrogensquarate monohydrate (CSD refcode: CONVAD) [15] and the hydrogensquarate of the α -amino acid derivative L-leucineamide (CSD refcode: YUKFUG) [14], isolated hydrogensquarate ions surrounded by the respective cations are observed. Interestingly, in the hemihydrate structure of the hydrogensquarate of the non-proteinogenic α -amino acid L-canavanine (CSD refcode: HIVSUA) [10], the hydrogensquarate are 1,2- and 1,3-connected through O-H \cdots O hydrogen bonds in an alternating fashion, resulting in a zigzag chain.

CONCLUSIONS

We have synthesized and structurally characterized hydrogensquarates of enantiopure L-leucine and racemic DL-leucine. The former, compound **1**, is a monohydrate and the latter, compound **2**, is solvent-free. The present study expands the series of structurally characterized squaric acid salts of the proteinogenic amino acids. As required by the enantiopure chiral L-leucinium ion, **1** crystallizes in a Sohncke space group. The entire crystal structure, however, fits 94% with *pseudo* centrosymmetry. In both **1** and **2**, the hydrogensquarate ions exhibit a 1,3-chain (β -chain) hydrogen bonding pattern. It is expected that the present study sparks future research into the properties of the compounds studied

and further investigations on the solid-state supra-molecular chemistry of squaric acid salts of amino acids in general.

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КРИСТАЛНИ СТРУКТУРИ НА L-ЛЕВЦИНИЕВ ХИДРОГЕНСКВАРАТ МОНОХИДРАТ И DL-ЛЕВЦИНИЕВ ХИДРОГЕНСКВАРАТ

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(Резюме)

Представени са кристалните структури на L-левциниево хидрогенскварат монохидрат (**1**) и DL-левциниево хидрогенскварат (**2**). Съединение **1** кристализира в моноклинна пространствена група $P2_1$, като асиметричната единица се състои от два левциниеви катиона и два хидрогенскваратни аниона ($Z = 4$, $Z' = 2$) и показва псевдоинверсионна симетрия. Кристалната структура на **1** се характеризира с две кристалографски различно подредени β -вериги от хидрогенскваратни йони, свързани с водни молекули чрез водородни връзки, обградени от свързани с водородни връзки L-левциниеви йони, което води до образуването на слоева структура със сложни $O-H \cdots O$ и $N-H \cdots O$ водородни връзки. Съединение **2** кристализира в моноклинна пространствена група $P2/n$ със $Z = 4$. Подобно на **1**, хидрогенскваратните аниони образуват β -вериги в кристалната структура. β -веригите са свързани с водородни връзки с DL-левциниевия йон, като по този начин се получава сложна структура от слоеве, свързани с $O-H \cdots O$ и $N-H \cdots O$ водородни връзки.