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Crystal structure of seleno-L-cystine dihydrochloride

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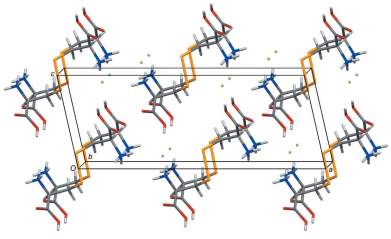
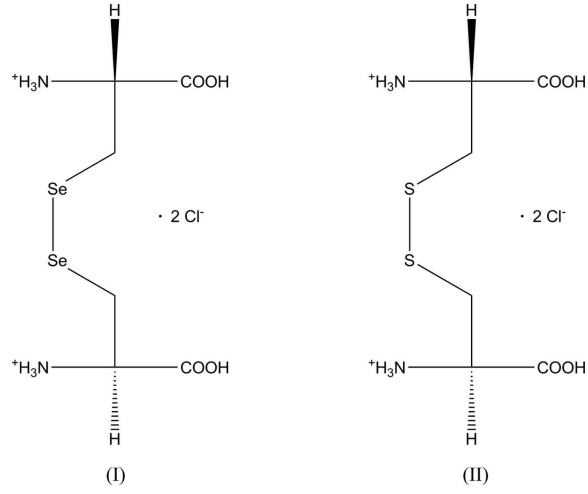
Numerous crystal structures are available for the dimeric amino acid cystine. In proteins it is formed by oxidation of the –SH thiol groups of two closely spaced cysteine residues, resulting in the formation of a familiar disulfide bridge. The title compound [systematic name: (*R*,*R*)-1,1′-dicarboxy-2,2′-(diselanediyl)-diethanaminium dichloride], $C_6H_{14}N_2O_4Se_2^{2+}\cdot 2Cl^-$, is the first example of a small molecule structure of the biologically important analogue with a $-CH_2-Se-Se-CH_2-$ bridging unit. Bond lengths and angles of seleno-L-cystine dihydrochloride and its isotypic sulfur analogue L-cystine dihydrochloride are compared.

1. Chemical context

In addition to the 20 amino acids directly encoded by the genetic code, three more are incorporated into proteins during translation. These three, selenocystine, pyrrolysine and *N*-formylmethionine, are considered to belong to a group of 23 proteinogenic amino acids. The UGA codon, normally a stop codon, is made to encode selenocysteine by the presence of a selenocysteine insertion sequence (SECIS) in the mRNA (Kryukov *et al.*, 2003).

Analogous to the common sulfur analogue cysteine, selenocysteine dimerizes through the formation of an Se—Se bridge to selenocystin, a substance that has received considerable attention recently for its anticancer efficacy (Yu *et al.*, 2015) as well as its potential in the prevention of cardiovascular and neurodegenerative diseases (Weekley & Harris, 2013).





In the Cambridge Structural Database (CSD, version 5.36; Groom & Allen, 2014) there are about 80 distinct structures of cystine deposited, either as an amino acid, a modified amino

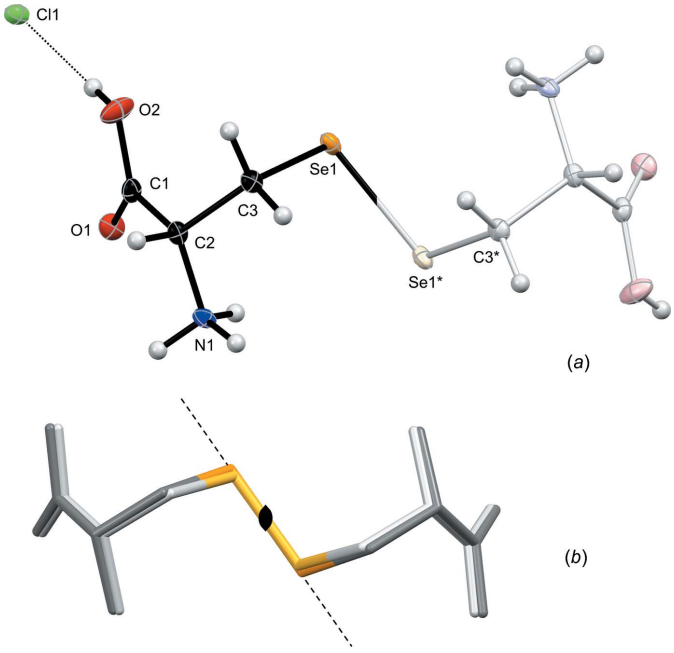


Figure 1
(*a*) The molecular structure of seleno-L-cystine dihydrochloride. The right-hand part, coloured in a light tone, is generated by application of twofold rotation symmetry in space group *C*2; Se1*, C3* *etc* are generated by the symmetry code $-x+1, y, -z$. Displacement ellipsoids are shown at the 50% probability level. (*b*) Best overlap between the structures of (I) (dark grey O, N and C atoms) and (II) (light grey; Leela & Ramamurthi, 2007) with a root-mean-square deviation of 0.133 Å. The view is along the twofold rotation axis (lens-shaped symbol), the dashed line gives the direction of the *z* axis.

acid or as an integrate part of a peptide or another large organic molecule. In contrast, there are no entries for selenocystine (and also none for sulfur–selenium hybrids with a $-CH_2-S-Se-CH_2-$ bridge). To provide detailed structural information for this biologically important link, an investigation of its structure, in the dihydrochloride salt $C_6H_{14}N_2O_4Se_2^{2+}\cdot 2Cl^-$, (I), has been undertaken.

2. Structural commentary

The molecular structure of (I) is shown in Fig. 1*a*. A twofold rotation axis relates the two parts of the molecule. The crystal packing is depicted in Fig. 2, with molecules stacked on top of each other along the 5.2529 (4) Å monoclinic axis. Compound (I) is isotypic with the structure of L-cystine dihydrochloride, (II) (Gupta *et al.*, 1974; Jones *et al.*, 1974; Leela & Ramamurthi, 2007), but not with the structure of L-cystine dihydrobromide (Anbuchezhiyan *et al.*, 2010), which forms a related packing arrangement but crystallizes in the orthorhombic space group $P2_12_12$. The disulfide/diselenide bridges adopt helical conformations in all three structures, characterized by having *gauche* $-C-C-X-X-$, $-C-X-X-C-$ and $-X-X-C-C-$ torsion angles (X = S or Se) of the same sign, in this case between −81 and −89° [Table 1; $-C-C-X-X-$ = $-X-X-C-C-$ by symmetry]. Geometric parameters for (I) and (II) are furthermore compared in Table 1 with average values from 16 acyclic $-CH_2-Se-Se-CH_2-$ links in non-amino acid structures retrieved from the CSD (Groom & Allen, 2014). The bond lengths and bond angles of (I) are similar to those in the previous seleno structures. The most important differences with respect to (II) [X-ray data at 173 K: a = 18.4405 (15), b = 5.2116 (6), c = 7.2191 (6) Å, β = 103.856 (6)°; Leela & Ramamurthi, 2007] are (obviously) the two Se—Se and S—S bond lengths, with modest changes for bond angles and torsion angles. Concerning the dimensions of the unit cell, there is above all an increase in the length of the cell edge a (+0.364 Å, 2%) due to longer C—Se than C—S bonds. An equivalent, anticipated effect on c as a result of the increased length of the Se—Se bond, which runs parallel to the z axis, is effectively counteracted by a 2.52° decrease for the two C—Se—Se angles along the bridge compared to the C—S—S angles, see: Fig. 1*b* and Table 1. The length of the short monoclinic axis b is determined by direct stacking of amino acid molecules, for which the S-to-Se substitution has less impact since neither is involved in any close intermolecular contacts.

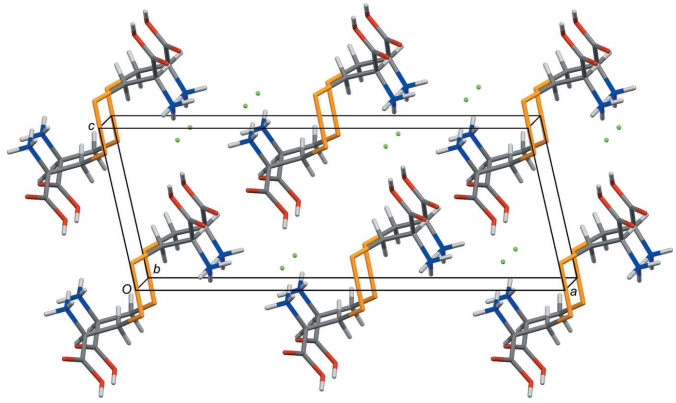


Figure 2
The crystal packing of seleno-L-cystine dihydrochloride viewed approximately along the *b* axis.

Table 1
Geometric parameters (Å, °) of diselenide and disulfide bridges.

Compound	C—Se/C—S	Se—Se/S—S	C—C—Se/S	C—Se/S—Se/S	C—C—Se/S—Se/S	C—Se/S—Se/S—C
(I)	1.9671 (18)	2.3213 (4)	113.96 (12)	100.88 (5)	−88.72 (12)	−83.05 (10)
Average[a]	1.967	2.310	114.17	101.29		
(II)[b]	1.817	2.040	114.48	103.40	−89.04	−81.04

Notes: (*a*) average of 16 $-CH_2-Se-Se-CH_2-$ bridges in acyclic non-amino acid structures; (*b*) Leela & Ramamurthi (2007).

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···Cl1^{i}	0.91	2.25	3.1425 (16)	167
N1—H2···Cl1^{ii}	0.91	2.40	3.2110 (18)	149
N1—H3···Cl1^{iii}	0.91	2.32	3.1794 (15)	157
O2—H4···Cl1	0.79 (6)	2.22 (6)	3.0080 (19)	172 (4)
C2—H21···O1^{iv}	1.00	2.39	3.292 (2)	150
C2—H21···O1^{iii}	1.00	2.55	3.216 (2)	124

Symmetry codes: (i) $x, y+1, z-1$; (ii) $x, y, z-1$; (iii) $-x+\frac{3}{2}, y+\frac{1}{2}, -z+1$; (iv) $x, y+1, z$.

3. Supramolecular features

The four strong hydrogen bonds with N—H and O—H donors all have Cl^- as the acceptor atom (Fig. 3*a*). The geometric parameters of the hydrogen bonds listed in Table 2 are almost identical to those of (II). There is also a three-centre interaction with a C^{α}—H donor and two carbonyl oxygen atoms as acceptors, Fig. 3*b*.

4. Synthesis and crystallization

Selenocystine has very low solubility in water as well as in organic solvents, including trifluoroethanol and 1,1,1,3,3,3-hexafluoropropan-2-ol, so a saturated solution was prepared in 0.1 *M* NaOH solution. 100 µl of this solution was pipetted into a small test tube (5 × 50 mm) to which a small amount of BTB pH indicator was added. The tube was sealed with parafilm punctured with a needle (one small hole) and placed inside a larger tube with concentrated hydrochloric acid. After 15 h the colour had shifted from blue to green, and small crystals of the hydrochloride could be harvested.

5. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. The position of the carboxyl H atom was restrained to the plane defined by O1, O2, C1 and C2; other H atoms were positioned with idealized geometry with fixed C/N—H distances for NH_3, CH_2 (methylene) and CH (methine) groups of 0.91, 0.99 and 1.00 Å, respectively.

Table 3
Experimental details.

Crystal data	
Chemical formula	$C_6H_{14}N_2O_4Se_2^{2+}\cdot 2(Cl^-)$
M_r	407.02
Crystal system, space group	Monoclinic, *C*2
Temperature (K)	100
a, *b*, *c* (Å)	18.8045 (16), 5.2529 (4), 7.2719 (6)
β (°)	102.219 (1)
V (Å^3)	702.03 (10)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	5.65
Crystal size (mm)	0.85 × 0.08 × 0.07
Data collection	
Diffractometer	Bruker D8 Advance single-crystal CCD
Absorption correction	Multi-scan (*SADABS*; Bruker, 2014)
T_{min}, T_{max}	0.514, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	11089, 4209, 4080
R_{int}	0.024
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.908
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.023, 0.062, 1.10
No. of reflections	4209
No. of parameters	78
No. of restraints	3
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	4.55, −0.87
Absolute structure	Flack *x* determined using 1708 quotients (Parsons *et al.*, 2013)
Absolute structure parameter	0.044 (4)

Computer programs: *APEX2* and *SAINT* (Bruker, 2014), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2014* (Sheldrick, 2015*b*) and *Mercury* (Macrae *et al.*, 2008).

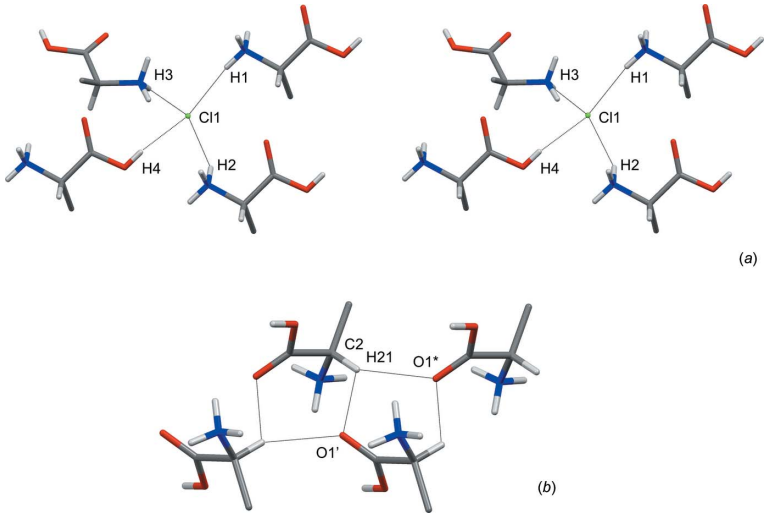


Figure 3
(*a*) Stereodrawing showing the coordination of hydrogen-bond donors around a Cl^- anion (see Table 2 for symmetry operators). (*b*) Tape motif along the *b* axis generated from C^{α}—H···O hydrogen bonds. O1* is at ($x, y+1, z$), O1′ at ($-x+\frac{3}{2}, y+\frac{1}{2}, -z+1$). Side chains have been truncated beyond C^{β}.

Free rotation was permitted for the ammonium group. U_{iso}(H) values were set to 1.2U_{eq} of the carrier atom, or 1.5U_{eq} for the ammonium group.

A rather large residual peak in the electron density map, with $\Delta\rho_{max}$ = 4.55 e Å^{-3}, remained after completion of the refinement. This peak is located on the twofold rotation axis at the center of the Se—Se bond, and evidently reflects bonding electrons. As a test, an extra isotropic C atom was introduced close to the axis. Its occupancy was subsequently refined to 0.17 (equivalent to one electron), and the *R*-factor fell from 0.0233 to 0.0180.

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Crystal structure of seleno-L-cystine dihydrochloride

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Computing details

Data collection: *APEX2* (Bruker, 2014); cell refinement: *SAINT* (Bruker, 2014); data reduction: *SAINT* (Bruker, 2014); program(s) used to solve structure: *SHELXT* (Sheldrick, 2015*a*); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015*b*); molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL2014* (Sheldrick, 2015*b*).

(*R*,*R*)-1,1′-Dicarboxy-2,2′-(diselanediyl)diethanaminium dichloride

Crystal data

$C_6H_{14}N_2O_4Se_2^{2+}\cdot 2(Cl^-)$
M_r = 407.02
Monoclinic, *C*2
a = 18.8045 (16) Å
b = 5.2529 (4) Å
c = 7.2719 (6) Å
β = 102.219 (1)°
V = 702.03 (10) Å^3
Z = 2
F(000) = 396
D_x = 1.925 Mg m^{-3}
Mo *Kα* radiation, *λ* = 0.71073 Å
Cell parameters from 9938 reflections
θ = 2.2–40.2°
μ = 5.65 mm^{-1}
T = 100 K
Needle, colourless
0.85 × 0.08 × 0.07 mm

Data collection

Bruker D8 Advance single-crystal CCD diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
Detector resolution: 8.3 pixels mm^{-1}
Sets of exposures each taken over 0.5° *ω* rotation scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2014)
T_{min} = 0.514, T_{max} = 1.000
11089 measured reflections
4209 independent reflections
4080 reflections with $I > 2\sigma(I)$
R_{int} = 0.024
θ_{max} = 40.2°, θ_{min} = 2.2°
h = −34→34
k = −9→9
l = −13→13

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.023
$wR(F^2)$ = 0.062
S = 1.10
4209 reflections
78 parameters
3 restraints
Hydrogen site location: inferred from neighbouring sites
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0169P)^2 + 0.004P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 4.55 e Å^{-3}
$\Delta\rho_{min}$ = −0.87 e Å^{-3}
Absolute structure: Flack *x* determined using 1708 quotients (Parsons *et al.*, 2013)
Absolute structure parameter: 0.044 (4)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
Se1	0.50147 (2)	0.56610 (5)	0.16037 (2)	0.01306 (4)
Cl1	0.65288 (2)	0.16979 (8)	0.87546 (6)	0.01345 (7)
O1	0.69775 (8)	0.3451 (3)	0.4104 (2)	0.0158 (2)
O2	0.62968 (9)	0.5697 (5)	0.57259 (19)	0.0225 (3)
H4	0.6356 (18)	0.454 (12)	0.644 (6)	0.058 (15)*
N1	0.67823 (8)	0.6777 (3)	0.1266 (2)	0.0125 (2)
H1	0.6681	0.8028	0.0384	0.019*
H2	0.6563	0.5305	0.0787	0.019*
H3	0.7272	0.6536	0.1591	0.019*
C1	0.66257 (8)	0.5306 (3)	0.4320 (2)	0.0125 (3)
C2	0.65058 (9)	0.7531 (3)	0.2961 (2)	0.0114 (2)
H21	0.6808	0.8988	0.3574	0.014*
C3	0.57160 (9)	0.8414 (3)	0.2457 (3)	0.0123 (2)
H31	0.5667	0.9713	0.1451	0.015*
H32	0.5592	0.9238	0.3573	0.015*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Se1	0.00843 (6)	0.01357 (7)	0.01686 (7)	−0.00112 (6)	0.00199 (4)	0.00422 (7)
Cl1	0.01334 (15)	0.01271 (15)	0.01538 (15)	0.00216 (12)	0.00550 (12)	0.00565 (12)
O1	0.0175 (6)	0.0106 (5)	0.0193 (6)	0.0028 (4)	0.0037 (5)	0.0040 (4)
O2	0.0349 (7)	0.0201 (6)	0.0146 (5)	0.0104 (8)	0.0100 (5)	0.0067 (7)
N1	0.0104 (5)	0.0118 (5)	0.0159 (5)	0.0005 (4)	0.0045 (4)	0.0045 (5)
C1	0.0125 (5)	0.0113 (7)	0.0126 (6)	0.0005 (4)	0.0000 (4)	0.0034 (4)
C2	0.0114 (6)	0.0083 (5)	0.0138 (6)	0.0003 (5)	0.0011 (5)	0.0021 (5)
C3	0.0125 (6)	0.0096 (5)	0.0147 (6)	0.0022 (5)	0.0029 (5)	0.0019 (5)

Geometric parameters (Å, º)

Se1—C3	1.9671 (18)	N1—H2	0.9100
Se1—Se1^{i}	2.3213 (4)	N1—H3	0.9100
O1—C1	1.206 (2)	C1—C2	1.516 (2)
O2—C1	1.319 (2)	C2—C3	1.525 (2)
O2—H4	0.79 (6)	C2—H21	1.0000
N1—C2	1.490 (2)	C3—H31	0.9900
N1—H1	0.9100	C3—H32	0.9900
C3—Se1—Se1^{i}	100.88 (5)	N1—C2—C3	112.00 (14)

C1—O2—H4	112 (4)	C1—C2—C3	113.22 (14)
C2—N1—H1	109.5	N1—C2—H21	107.9
C2—N1—H2	109.5	C1—C2—H21	107.9
H1—N1—H2	109.5	C3—C2—H21	107.9
C2—N1—H3	109.5	C2—C3—Se1	113.96 (12)
H1—N1—H3	109.5	C2—C3—H31	108.8
H2—N1—H3	109.5	Se1—C3—H31	108.8
O1—C1—O2	125.92 (18)	C2—C3—H32	108.8
O1—C1—C2	123.24 (17)	Se1—C3—H32	108.8
O2—C1—C2	110.84 (16)	H31—C3—H32	107.7
N1—C2—C1	107.72 (14)		
O1—C1—C2—N1	9.3 (2)	N1—C2—C3—Se1	70.66 (16)
O2—C1—C2—N1	−170.64 (15)	C1—C2—C3—Se1	−51.39 (17)
O1—C1—C2—C3	133.72 (17)	C2—C3—Se1—Se1^{i}	−88.72 (12)
O2—C1—C2—C3	−46.24 (19)	C3—Se1—Se1^{i}—C3^{i}	−83.05 (10)

Symmetry code: (i) −*x*+1, *y*, −*z*.

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···Cl1^{ii}	0.91	2.25	3.1425 (16)	167
N1—H2···Cl1^{iii}	0.91	2.40	3.2110 (18)	149
N1—H3···Cl1^{iv}	0.91	2.32	3.1794 (15)	157
O2—H4···Cl1	0.79 (6)	2.22 (6)	3.0080 (19)	172 (4)
C2—H21···O1^{v}	1.00	2.39	3.292 (2)	150
C2—H21···O1^{iv}	1.00	2.55	3.216 (2)	124

Symmetry codes: (ii) *x*, *y*+1, *z*−1; (iii) *x*, *y*, *z*−1; (iv) −*x*+3/2, *y*+1/2, −*z*+1; (v) *x*, *y*+1, *z*.