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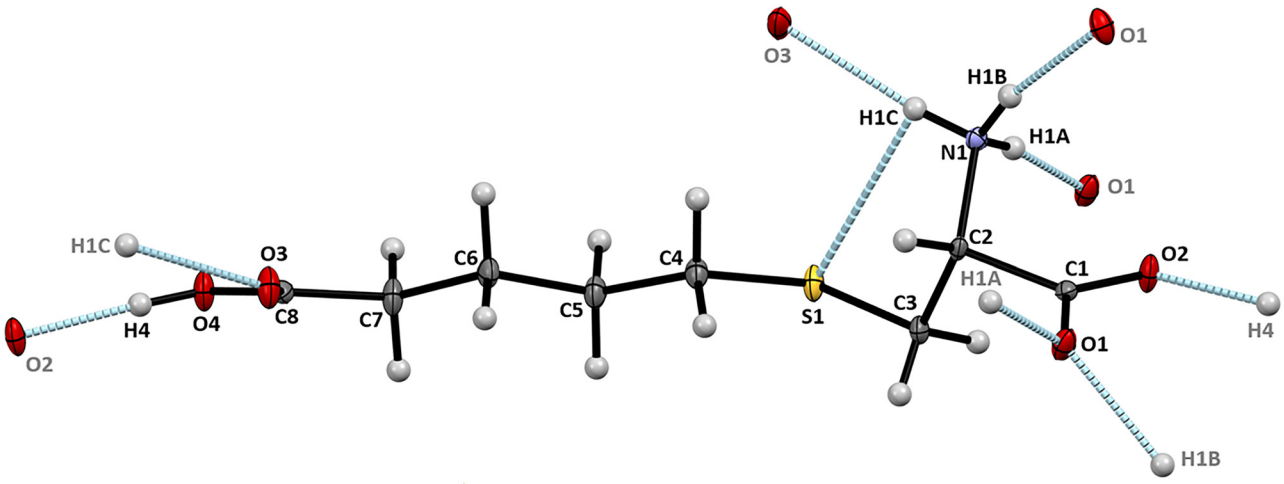
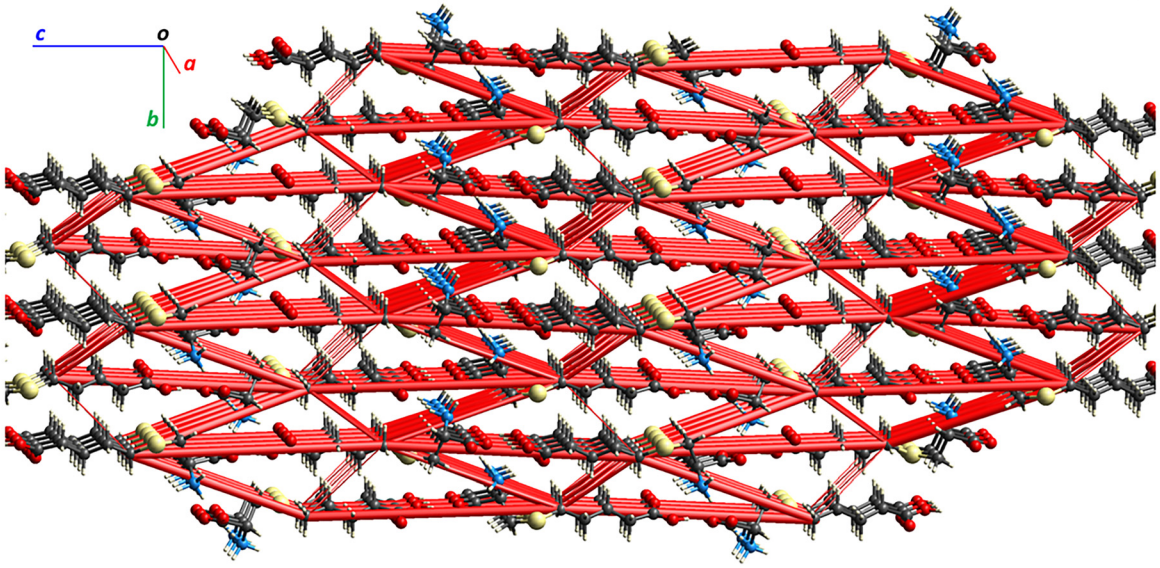
Crystal structure of *S*-(4-carboxybutyl)-*L*-cysteine





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Abstract

$C_8H_{15}NO_4S$, orthorhombic, $P2_12_12_1$ (no. 19), a = 5.0215 (3) Å, b = 7.0392 (5) Å, c = 28.0593 (19) Å, V = 991.82 (11) Å^3, Z = 4, $R_{gt}(F)$ = 0.0462, $wR_{ref}(F^2)$ = 0.0899, T = 100 K.

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The molecular structure, hydrogen bonds, a part of the title crystal structure and the electrostatic energy framework are shown in the figure. Tables 1 and 2 contain details on the crystal structure as well as measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

1 Source of materials

L–Cysteine (12.1 g, 0.1 mol) and 4-pentenoic acid (11 g, 0.11 mol) were dissolved in 500 mL of water containing 4.4 g (0.11 mol) of NaOH and left overnight at room temperature.

Table 1: Data collection and handling.

Crystal:	Colourless plate
Size:	0.18 × 0.10 × 0.01 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.32 mm^{-1}
Diffractometer, scan mode:	Bruker APEX II, φ and ω
θ_{max}, completeness:	29.0°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	13,433, 2638, 0.048
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 2473
$N(param)_{refined}$:	174
Programs:	Bruker,[1] SHELX,[2,3] Olex2[4]

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
S1	0.45191 (15)	0.04882 (12)	0.12329 (2)	0.01319 (17)
O1	1.1723 (4)	−0.0418 (4)	0.24142 (7)	0.0136 (4)
O2	0.7671 (4)	−0.0568 (4)	0.27473 (7)	0.0134 (4)
C1	0.9256 (6)	−0.0711 (4)	0.24029 (9)	0.0087 (5)
O3	0.8845 (4)	−0.0766 (3)	−0.11118 (7)	0.0165 (5)
O4	0.5098 (4)	0.0376 (4)	−0.14442 (7)	0.0144 (5)
C5	0.5356 (7)	0.0382 (5)	0.02807 (10)	0.0139 (6)
H5A	0.345 (8)	−0.003 (5)	0.0283 (12)	0.017*
H5B	0.547 (8)	0.177 (5)	0.0277 (12)	0.017*
C4	0.6598 (7)	−0.0325 (5)	0.07451 (10)	0.0128 (6)
H4A	0.842 (7)	0.014 (5)	0.0795 (12)	0.015*
H4B	0.661 (8)	−0.173 (5)	0.0759 (12)	0.015*
C7	0.5341 (7)	0.0446 (5)	−0.06108 (9)	0.0141 (6)
H7A	0.341 (8)	0.011 (5)	−0.0629 (12)	0.017*
H7B	0.534 (8)	0.183 (5)	−0.0596 (12)	0.017*
C6	0.6665 (6)	−0.0385 (5)	−0.01705 (10)	0.0130 (6)
H6A	0.861 (7)	−0.009 (5)	−0.0169 (12)	0.016*
H6B	0.642 (7)	−0.180 (5)	−0.0183 (12)	0.016*
N1	0.5859 (5)	−0.2606 (4)	0.19879 (9)	0.0088 (5)
C2	0.7987 (6)	−0.1157 (4)	0.19187 (10)	0.0085 (5)
H2	0.928 (7)	−0.169 (5)	0.1700 (11)	0.010*
C3	0.6849 (6)	0.0706 (5)	0.17204 (10)	0.0114 (6)
H3A	0.827 (7)	0.151 (5)	0.1641 (12)	0.014*
H3B	0.582 (7)	0.124 (5)	0.1962 (12)	0.014*
C8	0.6645 (6)	−0.0048 (4)	−0.10798 (10)	0.0105 (6)
H1A	0.461 (8)	−0.207 (5)	0.2132 (12)	0.012 (9)*
H1B	0.657 (8)	−0.362 (6)	0.2149 (14)	0.026 (11)*
H1C	0.524 (10)	−0.301 (6)	0.1713 (16)	0.039*
H4	0.608 (9)	0.034 (7)	−0.1716 (15)	0.039*

The solution was further acidified with 6.6 mL (0.11 mol) of glacial acetic acid and allowed to stand at 4°C for next 3 days. Colourless plates of chromatographically pure crystalline CBC have formed during this time; the crystalline mass was filtered out, washed with cold 95 % ethanol, dried on air and used for subsequent diffraction studies. Element analysis. Calc. for $C_8H_{15}NO_4S$: N, 6.33 %. Found: N, 6.37 %. Exact mass of the $[M+H]^+$ ion in ESI mass-spectrum. Calc. for $C_6H_{12}NO_4S$: *m*/*z* 222.07. Found: *m*/*z* 222.08.

2 Experimental details

The Flack absolute structure parameter determined (−0.02 (3) for 1277 quotients[5]) is consistent with the (2*R*) configuration, which was assigned for this molecule on the basis of the known configuration for the starting material L-cysteine. Data were corrected for Lorentz, polarization, and absorption effects. The hydroxyl and ammonium hydrogen atoms were located in difference Fourier maps and were allowed to refine freely. The remaining H-atoms were placed at calculated positions and included in the refinement using a riding model. All hydrogen atom thermal parameters were constrained to ride on the carrier atoms (U_{iso}(methine H) = 1.2 U_{eq} and U_{iso}(methyl H) = 1.5 U_{eq}).

3 Comment

The title compound, *S*-(4-carboxybutyl)-*L*-cysteine (CBC), is a synthetic analog of two important biologically active *S*-carboxyalkylcysteines, a mucolytic drug *S*-carboxymethyl–L-cysteine (carbocisteine, CMC) and a natural insecticide from legumes *S*-(2-carboxyethyl)–L-cysteine (*β*–CEC).[6] Both CMC and *β*–CEC are thioether-containing amino acids and, similarly to methionine, possess the antioxidant capacity that could be employed in clinics.[7] Recently,[8,9] we have demonstrated that CMC and *β*–CEC can protect DNA from oxidative degradation, protect airway and kidney cells from cytotoxic platinum drugs or copper oxide nanoparticles, mitigate pro-inflammatory signaling in the cells. In continuation of our studies on antioxidant amino acids,[8–10] we have synthesized CBC and report here its molecular and crystal structure.

The asymmetric unit of the title structure contains one molecule of CBC, shown in the Figure generated by Mercury.[11] The valence bond lengths and angles are in the expected ranges. The molecule of this dicarboxylic amino acid exists as a zwitterion, with positively charged protonated α-amino group and negatively charged deprotonated α-carboxylic group. Most of non-hydrogen atoms, with exception of N1, O1, and C3, are located within 0.3 Å from a molecular plane. There is a weak intramolecular hydrogen bond between the ammonium donor and thioether acceptor heteroatoms (N1···S1 = 3.112 (3) Å, H1*C*···S1 = 2.83 (4) Å, N1–H1*C*···S1 = 101 (3)°). The conventional hydrogen bonding in crystal structure of CBC is extensive, involves all heteroatoms and forms network

layers propagating in parallel to (001). Each layer is formed by a system of intercrossing chains. In the [100] direction, the heterodromic chain ···H1*C*–N1–H1*B*···O1–C1–O2···H4–O4–C8–O3···H1*C*–N1–H1*B*··· incorporates the shortest heteroatom contact formed between the α- and η-carboxylic groups (O4···O2 = 2.534 (3) Å, H4···O2 = 1.64 (4) Å, O4–H4···O2′ = 168 (4)°, ’ = 3/2–x, –y, –1/2 + *z*). In the [010] direction, the antidromic chains ···H1*A*–N1–H1*B*···O1···H1*A*–N1–H1*B*···O1··· feature bifurcated H-bonds at the O1 atoms. The network is reinforced by the short C3–H3*A*···O4 and C4–H4*B*···O3 contacts contributing to the polar interactions in the crystal structure, as well.

To account for all interactions contributing to the crystal structure, we have performed DFT calculations, at the B3LYP/6–31 G(d,p) theory level,[12,13] of the electrostatic, dispersion, polarization, and repulsion energies in the CBC crystal structure. According to the calculations, the interactions between pairs of molecules linked via the N1–H1*B*···O1″ hydrogen bond (” = 2–x, –1/2 + y, 1/2–z) provided the largest contribution, about 30 %, to the lattice energy, with the electrostatic interactions contributing the most for the attractive forces between neighbouring molecules of CBC (*i.e.* E_{elstat} = –90.3 kJ/mol, $E_{energy\text{-}dispersive}$ = –15 kJ/mol for 2 – x, –1/2 + y, 1/2 – z). The spatial distribution of the energetically most significant interactions is illustrated in the Figure, showing the electrostatic energy framework as red cylinders penetrating the crystal lattice of CBC. The cylinders connect centroids of the interacting molecules, and their diameters are proportional to the total energies of the interactions, with the 10 kJ/mol cut-off, for clarity. The most extensive intermolecular interactions occur in the directions parallel to [001]. To estimate the crystal structure energy, the total energies of unique pairwise interactions between molecules were integrated, thus yielding E_{cryst} = –353.5 kJ/mol for the CBC crystal.

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