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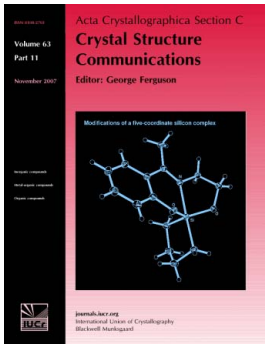

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Crystallographic rationalization of the reactivity and spectroscopic properties of (2*R*)-*S*-(2,5-dihydroxyphenyl)cysteine

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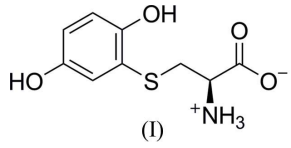
At 150 K, the title compound, $C_9H_{11}NO_4S$, crystallizes in the orthorhombic form as a zwitterion and has a low *gauche* conformation [χ = −46.23 (16)°] for an acyclic cysteine derivative. A difference in bond length is observed for the alkyl C—S bond [1.8299 (15) Å] and the aryl C—S bond [1.7760 (15) Å]. The $-NH_3^+$ group is involved in four hydrogen bonds, two of which are intermolecular and two intramolecular. The compound forms an infinite three-dimensional network constructed from four intermolecular hydrogen bonds. Characterization data (^{13}C NMR, IR and optical rotation) are reported to supplement the incomplete data disclosed previously in the literature.

Comment

(2*R*)-*S*-(2,5-Dihydroxyphenyl)cysteine, (I), is the adduct formed by nucleophilic attack of cysteine thiol on *p*-benzoquinone. It was investigated as a reducing agent (Hatanaka *et al.*, 1972) and has been reported in the context of a study on inhibitors of betacyanin synthesis (Hayashi & Koshimizu, 1979). It has also been the subject of a mass spectrometry study (d'Ischia *et al.*, 1996). It is a very useful biochemical tool and has been used in the investigation of the metabolism of benzene, phenol and hydroquinone (Bratton *et al.*, 1997; Lunte & Kissinger, 1983) and of the metabolism of acetaminophen/paracetamol (Pascoe *et al.*, 1988; Axworthy *et al.*, 1988). It has been shown to be cytotoxic to melanoma cells (Yamada *et al.*, 1988) and it is believed that the mode of action is tyrosinase inhibition. Indeed, the tyrosinase inhibitory activity of (I) has been disclosed in a recent patent concerning the use of the compound as a skin-brightening agent (Wempe & Clauson, 2008). Applications of (I) in hair dyeing (Wenke & Prota, 1995) and permanent waving (Kubo & Schultz, 1994) have also been patented.

Concerning the synthesis of (I), an early reported procedure (Kuhn & Beinert, 1944) was subsequently reinvestigated (Crescenzi *et al.*, 1988) and it was found that, under certain conditions, a mixture of 1,4-benzothiazine oligomers may be formed in preference to the desired product. We undertook synthesis of (I) by addition of *p*-benzoquinone in ethanol to L-cysteine in H_2O (Hayashi & Koshimizu, 1979). Spectroscopic characterization of (I) to date has been incomplete. Thus, we report here the high-field ^{1}H and ^{13}C NMR spectra, IR spectrum and optical rotation of (I).



(I)

The asymmetric unit of (I) (Fig. 1) contains one molecule of (2*R*)-*S*-(2,5-dihydroxyphenyl)cysteine, which forms hydrogen bonds with every heteroatom except sulfur. The protonated amino group on its own forms two intramolecular hydrogen bonds, *viz.* N1—H1*B*···O2 and N1—H1*C*···O3, and two intermolecular hydrogen bonds, *viz.* N1—H1*A*···O1^{iii} and N1—H1*B*···O4^{iv} (symmetry codes as in Table 2). In combination with the two hydrogen-bond-forming OH groups of the hydroquinone moiety, this gives rise to an infinite three-dimensional network of N—H···O and O—H···O bonds. Details of these hydrogen bonds are given in Table 2 and the hydrogen-bond network is illustrated in Fig. 2. In the crystallographic literature only two other cysteine derivatives with a cyclic substituent on the S atom have been reported, 5-*S*-cysteinyluracil monohydrate (Williams *et al.*, 1977) and *S*-benzyl-L-cysteine (Troup *et al.*, 2001). Bond lengths in these cysteinyl units are very similar to the corresponding bond lengths found in (I).

The structure we report here serves to explain the reported reactivity trends of (I) and aspects of the characterization data obtained for (I) by other techniques, as well as to suggest an application for (I) in peptide engineering. Firstly, phenolic alkylthioethers such as (I) have been reported (Costantini *et al.*, 1994; d'Ischia *et al.*, 1995) to show a marked proclivity for undergoing UV-induced desulfurization *via* regiospecific alkyl C—S bond cleavage and to fragment in a similar fashion under

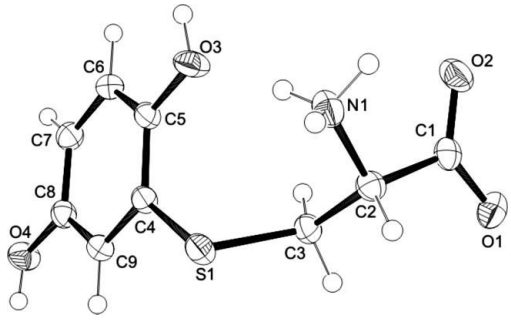


Figure 1
The molecular structure and atom-labelling scheme of (I). Displacement ellipsoids are depicted at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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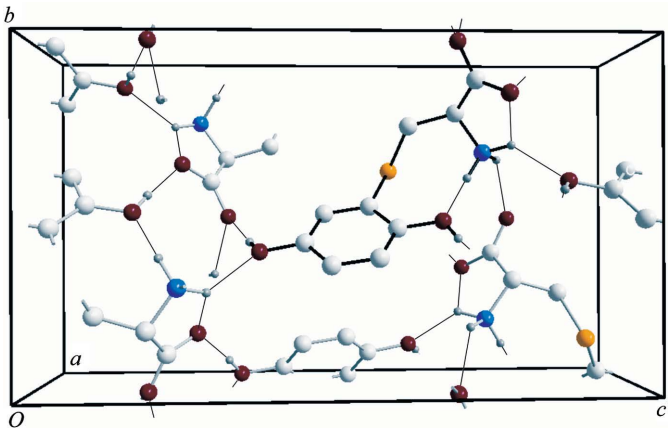

Figure 2
The hydrogen-bond network (thin lines) of (I).

conditions of mass spectrometric analysis (d'Ischia *et al.*, 1996). A rationale for the specific cleavage of the C3—S1 bond in this process may be derived from inspection of the crystal structure. Specifically, the observed C3—S1 bond length in (I) of 1.8299 (15) Å is appreciably longer than the C4—S1 bond length of 1.7760 (15) Å. Bond length and strength have previously been correlated for C—S bonds (Woodard *et al.*, 1976; Polenov *et al.*, 2006; Seidel *et al.*, 2007). Thus, it may be deduced that the C3—S1 bond in (I) is the weaker of the two C—S bonds, so rationalizing the observation that the C3—S1 bond is particularly susceptible to regiospecific scission.

Secondly, discrepancies between the ^{13}C NMR spectra for (I) and L-cysteine may be rationalized on the basis of the present crystal structure. The C3 methylene resonance is observed at δ = 34.5 p.p.m. for (I), but has been observed by us at δ = 25.5 p.p.m. for L-cysteine (both in DMSO-d_6; DMSO is dimethyl sulfoxide). This significant downfield shift ($\Delta\delta$ = 9.0 p.p.m.) upon introduction of the substituent on S implies that the electron-rich aryl ring exerts a deshielding effect. We propose this to be a consequence of the arene ring current and of conjugation of the S atom with the arene π-system: electron donation into the ring lowers the electron density on the S atom, deshielding the nucleus of the adjacent atom C3. The difference in observed bond lengths for C4—S1 and C3—S1 provides compelling evidence for higher bond order for the C4—S1 bond and hence for the deshielding effect detailed above (the inequivalence of the C4—S1 and C3—S1 bond lengths will persist in solution).

Thirdly, as can be seen in Table 1, the cysteine N1—C2—C3—S1 moiety adopts a very low *gauche* torsion angle of −46.23 (16)°, due to the intramolecular N1—H1*C*···O3 hydrogen bond. No lower N—C—C—S torsion angle has thus far been reported for an acyclic cysteine derivative. In this conformation, the small angle allows direct alignment of O3 with the N1—H1*C* bond for optimal hydrogen bonding. A similarly low N—C—C—S torsion angle has previously only been described in four structures of cysteine derivatives: −46.5 (2) and −47.8 (3)° for cysteine mandelic acid diastereomers (Fujii *et al.*, 2005), −48.2 (3)° for *S*-benzyl-L-cysteine (Troup *et al.*, 2001), 48.8° for *S*-carboxymethyl-L-cysteine (Mighell *et al.*, 1979) and 48.9 (3)° in L-cysteine L-tartrate monohydrate (Shan & Huang, 1999). It is noteworthy that the N1—C2—C3—S1 torsion angle that we have observed is similar to the values of −45.6 (3) and 48.8 (3)° reported (Ranganathan *et al.*, 2002) in a dimeric structure of a closely analogous L-cysteinylaryl derivative in which the N—C—C—S motif is explicitly constrained by incorporation into a seven-membered ring. This supports the conclusion that in the case of (I) it is the intramolecular hydrogen bond that is responsible for the anomalously low N—C—C—S torsion angle.

To conclude, it should be noted that this accurate structure constitutes an additional tool for rational peptide design. The OH functionality in the non-natural sulfur substituent of (I) results in a significant change in the N—C—C—S torsion angle in the amino acid moiety. Use of this non-natural amino acid with such an unusual torsion angle will allow the rational design of new peptides of defined secondary structure. Indeed, several oligopeptides containing (2*R*)-*S*-(2,5-dihydroxyphenyl)cysteine have been reported (Hansen *et al.*, 2001; Ahlfors *et al.*, 2003; Holmdahl *et al.*, 2008), although none has been characterized by crystallography so far. We anticipate that the low torsion angle will orient the polarized aromatic ring such that it will exhibit π–π interactions with appropriate proximate aryl residues (Waters, 2004), which will confer defined secondary structure on the peptide.

Experimental

The title compound was prepared as described previously (Hayashi & Koshimizu, 1979). The crude product was dissolved in refluxing ethanol–water (100 ml; 1:1 *v*/*v*) and filtered whilst hot. The filtrate was allowed to cool to room temperature and was stored at 277 K for 3 d to give (I) (yield 6.54 g, 77%) as a yellow crystalline solid of sufficient quality for crystal structure analysis. $[\alpha]_D^{25}$ +165° (*c* 1.0, 1 *M* HCl_{aq}); ^{1}H NMR (500 MHz, DMSO-d_6, 298 K): δ 8.50 (5H, *br s*, –OH and –NH), 6.84 (1H, *d*, *J* = 2.5 Hz, Ar–H), 6.71 (1H, *d*, *J* = 8.5 Hz, Ar–H), 6.54 (1H, *dd*, *J* = 8.5 and 2.5 Hz, Ar-H), 3.35 (1H, *dd*, *J* = 13.5 and 4.0 Hz, –S—CHH–), 3.31 (1H, *dd*, *J* = 8.5 and 4.5 Hz, –S—CH_2—CH–), 2.96 (1H, *dd*, *J* = 13.5 and 9.0 Hz, –S—CHH–); ^{13}C NMR (75.4 MHz, DMSO-d_6, 298 K): δ 169.6, 150.5, 149.4, 120.1, 118.0, 116.4, 115.4, 53.4, 34.5; IR (film, ν_{max}, cm^{-1}): 3093, 3000, 2692, 2581, 1630, 1578, 1440, 1388, 1339, 1251, 1206, 1132, 1051, 939, 904, 855, 820, 779, 659.

Crystal data

$C_9H_{11}NO_4S$
M_r = 229.25
Orthorhombic, $P2_12_12_1$
a = 5.1661 (1) Å
b = 10.3981 (2) Å
c = 18.2979 (3) Å
V = 982.92 (3) Å^3
Z = 4
Mo *K*α radiation
μ = 0.32 mm^{-1}
T = 150 K
0.40 × 0.38 × 0.38 mm

Data collection

Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
T_{min} = 0.882, T_{max} = 0.887
22623 measured reflections
2875 independent reflections
2507 reflections with $I > 2\sigma(I)$
R_{int} = 0.062

Table 1
Selected geometric parameters (Å, °).

S1—C4	1.7760 (15)	O2—C1	1.2517 (19)
S1—C3	1.8299 (15)	O3—C5	1.3779 (18)
N1—C2	1.491 (2)	O4—C8	1.3718 (16)
O1—C1	1.2527 (19)		
C4—S1—C3	99.59 (7)	C5—C4—S1	122.25 (11)
O2—C1—O1	127.29 (14)	C9—C4—S1	118.67 (11)
O2—C1—C2	117.22 (13)	O3—C5—C6	121.67 (13)
O1—C1—C2	115.47 (14)	O3—C5—C4	118.48 (13)
N1—C2—C3	110.81 (12)	O4—C8—C9	121.93 (14)
N1—C2—C1	109.13 (12)	O4—C8—C7	118.14 (14)
C2—C3—S1	113.81 (10)		
O2—C1—C2—N1	−9.67 (18)	N1—C2—C3—S1	−46.23 (16)
O1—C1—C2—N1	171.61 (13)	S1—C4—C5—O3	−2.47 (19)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O2^{i}	0.94 (3)	1.68 (3)	2.6214 (16)	177 (3)
O4—H4···O1^{ii}	0.82 (2)	1.82 (2)	2.6402 (18)	179 (2)
N1—H1*A*···O1^{iii}	0.88 (3)	2.24 (3)	2.8231 (17)	124 (2)
N1—H1*B*···O4^{iv}	0.96 (3)	2.11 (3)	2.8399 (18)	132 (2)
N1—H1*B*···O2	0.96 (3)	2.12 (3)	2.6223 (19)	111 (2)
N1—H1*C*···O3	0.95 (3)	1.88 (3)	2.822 (2)	175 (2)

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

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.077$
$S = 1.05$
2875 reflections
156 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.22$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}
Absolute structure: Flack (1983), with 1188 Friedel pairs
Flack parameter: −0.06 (6)

All H atoms attached to N and O atoms were located in a difference Fourier map and their positions and isotropic displacement parameters were refined freely. All other H atoms were placed in calculated positions and refined using a riding model, with C—H = 0.95 (aromatic), 0.99 (methylene) or 1.00 Å (methine) and U_{iso}(H) = $1.2U_{eq}$(C).

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *DIAMOND* (Brandenburg, 2005).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: MX3028). Services for accessing these data are described at the back of the journal.

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