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Crystallographic evidence of Gly-D,L-Met oxidation to its sulfoxide in the presence of gold(III): solid solution of the racemic mixture of two diastereoisomers

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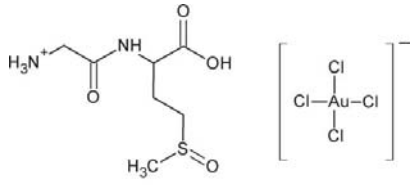
Crystallographic analysis of a solid solution of two diastereoisomers, *i.e.* ({(1*S*,*R*)-1-carboxy-3-[(*R*,*S*)-methylsulfinyl]propyl}aminocarbonyl)methanaminium tetrachloridoaurate(III) and ({(1*S*,*R*)-1-carboxy-3-[(*S*,*R*)-methylsulfinyl]propyl}aminocarbonyl)methanaminium tetrachloridoaurate(III), $(C_7H_{15}N_2O_4S)[AuCl_4]$, has shown that in the presence of gold(III), the methionine part of the Gly-D,L-Met dipeptide is oxidized to sulfoxide, and no coordination to the Au^{III} cation through the S atom of the sulfoxide is observed. In view of our observation, literature reports that methionine acts as an *N*,*S*-bidentate donor ligand forming stable gold(III) complexes require verification. Moreover, it has been demonstrated that crystallization of the oxidation product leads to a substantial 77:23 excess of both *S*-methionine/*R*-sulfoxide and *R*-methionine/*S*-sulfoxide over *S*-methionine/*S*-sulfoxide and *R*-methionine/*R*-sulfoxide. The presence of two different diastereoisomers at the same crystallographic site is a source of static disorder at this site.

Comment

The prominent role of methionine oxidation/reduction in aging and age-related degenerative diseases and in the regulation of cell function (Hoshi & Heinemann, 2001) stimulated our interest in the role of gold(III) halides in the oxidative process of the amino acid methionine and methionine-containing peptides. By reacting hydrogen tetrachloridoaurate(III) with the Gly-D,L-Met dipeptide and subjecting the final product of this reaction to X-ray analysis, we wished to verify the literature reports on the ability of gold(III) halides to oxidize methionine to its sulfoxide, and furthermore to find out whether the newly formed sulfoxide group has the ability to replace chloride ligands in the first coordination sphere of the gold(III) cation, in a manner similar to the coordination of methionine sulfoxide to platinum(II) (Freeman, 1977; Bruhn *et al.*, 1999; Ling *et al.*, 1993). It has been known for some time that gold(III) halides are able to oxidize sulfides (Natile *et al.*, 1976), disulfide bridges in albumin and insulin (Witkiewicz & Shaw, 1981), and methionine residues of ribonuclease (Isab & Sadler, 1977). The mechanism of this redox reaction has been investigated (Natile *et al.*, 1976; Vujačić *et al.*, 2009) but so far no crystallographic evidence for the reaction has been provided. We report herein the synthesis, isolation and X-ray analysis of the product of the reaction of hydrogen tetrachloridoaurate(III) with the Gly-D,L-Met dipeptide.



(I)

The product turned out to be the tetrachloridoaurate(III) salt, (I), of H^+Gly-Met sulfoxide. The crystal structure consists of discrete square-planar $[AuCl_4]^-$ anions and glycylmethionine sulfoxide cations (Fig. 1 and Table 1). The cations are disordered at the methionine side chain due to the presence, at the same crystallographic site, of two diastereomers differing in their configuration at the triply-bonded S atom. Consequently, the Gly-Met sulfoxide cations contain two asymmetric centres, one at a peptide C^{α} atom (designated as S_M or R_M)

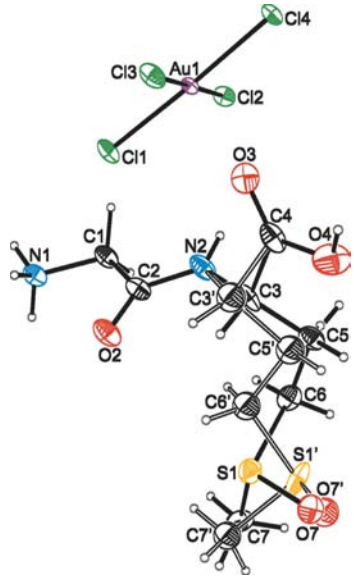


Figure 1
The asymmetric unit of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii. Primed and unprimed atoms connected by open and filled bonds, respectively, illustrate the disorder of the methionine sulfoxide side chain, caused by the presence at the same crystallographic site of both R_S and S_S isomers.

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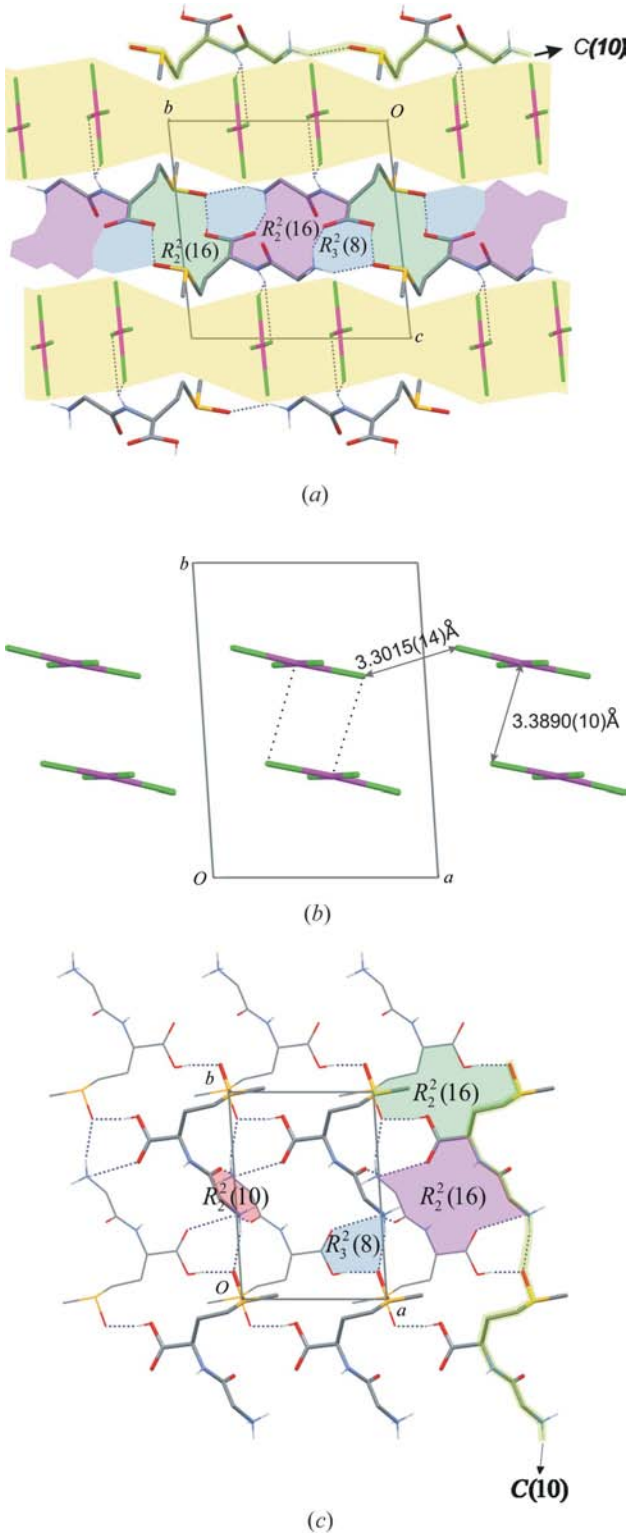

Figure 2
(*a*) Alternating cationic and anionic (001) layers situated at, respectively, $\frac{1}{2}$ and 0 along *c*. Hydrogen-bonding interactions are shown as dotted lines. The view is along the *a* axis. (*b*) The arrangement of the anionic $[AuCl_4]^-$ species within the (001) layer, with close Au···Cl and Cl···Cl distances indicated by arrows. Dotted lines indicate Au···Cl interactions. The view is along the *c* axis. (*c*) The undulating double molecular cationic layer in (001), viewed along the *c* axis. Thick and thin lines differentiate molecules situated at different *c* levels. Hydrogen-bonding interactions are shown as dotted lines.

and the other at the S atom (designated as S_S or R_S). The crystallization process is partially diastereoselective, leading to an excess of one of the two possible diastereoisomers for the reference molecule, *i.e.* S_M,R_S over S_M,S_S (Fig. 1), the ratio being 77:23. As the crystal is centrosymmetric, it contains equal amounts of the enantiomers of the two diastereoisomers, with the R_M,S_S:R_M,R_S ratio also being 77:23. Data collected for another crystal selected from the same sample provided a similar ratio of diastereoisomers, *viz.* 0.70:0.30. This crystallographic finding is in contrast with the report (Natile *et al.*, 1976) that the reaction of equimolar amounts of (*S*)-methionine and hydrogen tetrachloridoaurate(III) in water proceeds with total stereospecificity, providing *S*-methionine-*S*-sulfoxide as the sole product. The Gly-Met sulfoxide units of (I) exist as cations, with the N and C termini protonated. For the predominant conformer, the relative orientation of the linked units can be described by a set of three torsion angles, *viz.* $\psi_1 = 172.2\ (3)$, $\omega_1 = 173.8\ (4)$ and $\Phi_2 = -118.8\ (5)^\circ$. The methionine side chain in the prevalent diastereoisomer adopts a *gauche*,*gauche*,*trans* conformation (described by the set of torsion angles γ^1 = N2—C3—C5—C6, γ^2 = C3—C5—C6—S1 and γ^3 = C5—C6—S1—C7 listed in Table 1), while the minor diastereoisomer (defined by the corresponding primed atoms) adopts a *gauche*,*trans*,*trans* conformation.

The extended structure of (I) consists of alternating inorganic ($[AuCl_4]^-$) and organic (H^+Gly-Met sulfoxide) layers parallel to the (001) lattice planes and situated at, respectively, 0 and $\frac{1}{2}$ along the *c* axis (Fig. 2*a*). Within the inorganic layer, the closest Au···Cl distance [3.3890 (10) Å] is less than the sum of the van der Waals radii of the two atoms (3.41 Å; Bondi, 1964). Thus, the square-planar arrangement of the $[AuCl_4]^-$ anionic core is complemented into an elongated square pyramid. Two such square-pyramidal units related by a centre of symmetry at ($\frac{1}{2}$, $\frac{1}{2}$, 0) share two chloride anions, forming an $[Au_2Cl_8]^{2-}$ dimer with an Au···Au separation of 3.8862 (3) Å (Fig. 2*b*), similar to reported examples (Bourosh *et al.*, 2007; Schimansky *et al.*, 1998). These dimeric units, related by a unit translation along the *a* direction, form close interanionic Cl···Cl contacts of 3.3015 (14) Å (shorter than the sum of the van der Waals radii for Cl atoms of 3.50 Å). The ladders thus formed, repeated by a unit translation along the *b* direction, extend into layers parallel to the (001) lattice plane (Fig. 2*a*). In between these layers one finds undulating bimolecular layers consisting of H^+Gly-Met sulfoxide cations (Figs. 2*a* and 2*c*).

The crystal structure of (I) is stabilized by various types of hydrogen bonds (Table 2). The presence of competitive hydrogen-bond acceptors, such as chloride anions and sulfoxide O atoms, perturbs the hydrogen-bond pattern typical for dipeptides. The ammonium–carboxyl hydrogen bond, known in dipeptides as the $C(8)$ motif, now forms the centrosymmetric $R_2^2(16)$ ring motif (for graph-set notation, see, for example, Bernstein *et al.*, 1995). In addition, it constitutes part of the $R_3^2(8)$ ring pattern, the other constituents being the carboxyl–sulfoxide and the ammonium–sulfoxide hydrogen bonds. Furthermore, pairs of centrosymmetrically related

ammonium–amide and carboxyl–sulfoxide hydrogen bonds lead to the formation of $R_2^2(10)$ and $R_2^2(16)$ motifs. Only the ammonium–sulfoxide $C(10)$ chain joins molecules situated at the same *c* level. The other hydrogen bonds operate between molecules situated in two neighbouring organic layers, the components of a single bilayer (Fig. 2*c*). The abovementioned hydrogen bonds not only hold together molecules constituting the double-molecular organic layer, but also join together the organic and inorganic layers. Intermolecular interactions occur between the protonated N-terminus and the peptide N—H group, and three of the four chloride anions.

In conclusion, we have provided crystallographic evidence that the methionine part of the Gly-D,L-Met dipeptide is oxidized to sulfoxide in the presence of gold(III), and no coordination to the gold(III) centre through the S atom of the sulfoxide is observed. In view of these findings, the reported coordination of gold(III) by sulfur in methionine-containing peptides (Ivanova & Mitewa, 2004) requires verification, preferably by crystallographic methods. We have also demonstrated that the crystallization process is partially stereoselective and leads to a substantial excess of one of the two possible diastereoisomers differing in the configuration at the triply bonded S atom.

Experimental

Distilled water was demineralized and purified to a resistance greater than 10 MΩ cm^{-1}. All common chemicals were of reagent grade and were used without further purification. The title compound was obtained by mixing together in water equimolar amounts of $H[AuCl_4]\cdot 3H_2O$ (Aldrich) and glycyl-D,L-methionine (Sigma) in the pH range 1.5–2.0 (achieved by adding a few drops of nitric acid) at room temperature. The resulting solution was filtered and the filtrate left to stand at room temperature, allowing crystals of (I) to precipitate. These crystals were filtered off and dried. Elemental microanalysis was performed by the Microanalytical Laboratory, Faculty of Chemistry, University of Belgrade. Analysis found: C 15.31, H 2.70, N 4.96, S 5.52%; $C_7H_{15}AuCl_4N_2O_4S$ requires: C 14.96, H 2.69, N 4.98, S 5.71%; yield *ca* 40%. Not all products present in the reaction mixture have been identified, but deposits of metallic gold were clearly visible on the walls of the reaction vessel.

The ^{1}H NMR spectrum of a D_2O solution of (I) containing TSP (sodium trimethylsilylpropane-3-sulfonate) as the internal reference was recorded with a Varian Gemini 200 spectrometer; δ (p.p.m.): 3.91 (GlyCH_2, *s*), 2.71 (MetδCH_3, *s*), ∼2.40 (MetβCH_2, *m*), ∼3.00 (MetγCH_2, *m*). As the chemical shift of the singlet of the Gly-Met methyl H atoms is 2.11 p.p.m., the observed very intense singlet at 2.71 p.p.m. was assigned to the methyl H atoms of the Gly-Met sulfoxide. The remaining part of the ^{1}H NMR spectrum resembled that of the Gly-Met dipeptide measured under the same experimental conditions. That the singlet at 2.71 p.p.m. belongs to the methyl H atoms of the Gly-Met sulfoxide was confirmed by measuring the ^{1}H NMR spectrum for the pure dimethyl sulfoxide in D_2O in acidic solution.

In order to verify whether the presence of nitric acid could have played a role in the oxidation of methionine, the whole synthetic procedure has been repeated using hydrochloric acid instead of nitric acid. On the basis of ^{1}H NMR and preliminary X-ray data, the reaction product has been identified as that obtained in the presence of nitric acid.

Table 1
Selected torsion angles (°).

C2—N2—C3—C5	113.2 (5)	C2—N2—C3′—C5′	112.4 (11)
N2—C3—C5—C6	−60.0 (6)	N2—C3′—C5′—C6′	−69.7 (17)
C3—C5—C6—S1	−68.1 (5)	C3′—C5′—C6′—S1′	−164.6 (15)
C5—C6—S1—O7	−70.3 (5)	O7′—S1′—C6′—C5′	62 (2)
C5—C6—S1—C7	−177.5 (5)	C7′—S1′—C6′—C5′	169.1 (18)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H11N···Cl2^{i}	0.91	2.69	3.476 (4)	145
N1—H11N···Cl3^{ii}	0.91	2.78	3.392 (3)	126
N1—H12N···O7^{iii}	0.91	2.05	2.881 (7)	151
N1—H13N···O2^{iv}	0.91	2.07	2.811 (4)	137
N1—H13N···O3^{v}	0.91	2.44	2.942 (5)	115
N2—H2N···Cl2^{vi}	0.88	2.80	3.493 (4)	136
N2—H2N···Cl4^{vi}	0.88	2.88	3.604 (4)	141
O4—H4O···O7^{vii}	0.84	1.75	2.585 (7)	170

Symmetry codes: (i) $-x, -y+1, -z$; (ii) $x-1, y, z$; (iii) $x, y+1, z$; (iv) $-x, -y+1, -z+1$; (v) $-x+1, -y+1, -z+1$; (vi) $-x+1, -y+1, -z$; (vii) $-x+1, -y, -z+1$.

Crystal data

$(C_7H_{15}N_2O_4S)[AuCl_4]$
M_r = 562.04
Triclinic, $P\overline{1}$
a = 7.6250 (5) Å
b = 10.2576 (4) Å
c = 10.7160 (7) Å
α = 95.281 (4)°
β = 107.222 (6)°
γ = 92.001 (4)°
V = 795.46 (8) Å^3
Z = 2
Mo *K*α radiation
μ = 10.06 mm^{-1}
T = 130 K
0.30 × 0.20 × 0.03 mm

Data collection

Kuma KM-4 CCD κ-geometry diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2007)
T_{min} = 0.092, T_{max} = 1.000
5656 measured reflections
2756 independent reflections
2650 reflections with $I > 2\sigma(I)$
R_{int} = 0.015

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.016
$wR(F^2)$ = 0.042
S = 1.12
2756 reflections
201 parameters
34 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.53 e Å^{-3}
$\Delta\rho_{min}$ = −0.91 e Å^{-3}

The hydroxy H atom was positioned using the HFIX 147 facility in *SHELXL97* (Sheldrick, 2008). The other H atoms were also positioned geometrically and refined using the riding-model technique, with the following distance constraints: tertiary C—H = 1.00 Å, secondary C—H = 0.99 Å, methyl C—H = 0.98 Å, ammonium N—H = 0.91 Å, peptide N—H = 0.88 Å and hydroxy O—H = 0.84 Å. U_{iso}(H) values were set at 1.2U_{eq}(parent) or 1.5U_{eq}(parent) for methyl and ammonium groups. The side chain of the methionine sulfoxide was found to be disordered over two sites, representing stereoisomers differing in the configuration at the triply-bonded S atom (R_S or S_S). The occupancy factors were first refined freely with their sum constrained to unity. For the reference molecule, possessing an *S* configuration at the peptide C^{α} atom, the values refined to 0.77 and

0.23 for the unprimed (R_S) and primed (S_S) fragments, respectively. These values were kept fixed at the final stages of the refinement. As the investigated crystal is centrosymmetric, it contains equal numbers of molecules possessing an *R* configuration at the peptide C^{α} atom, for which the ratio of R_M,S_S and R_M,R_S isomers is of course the same, *i.e.* 77:23. For the major component, all non-H atoms were refined anisotropically, while for the minor component only the S atom was refined anisotropically. The remaining non-H atoms (C3′, C5′, C6′, C7′ and O7′) were given a common isotropic displacement parameter which refined to a value of 0.037 (3) $Å^2$. For the disordered fragment, which involves atoms C3, C5, C6, C7, O7 and S1 and their primed equivalents, the following restraints were applied to bond distances: C—N = S═O = 1.49 (2) Å, C—C = 1.53 (2) Å and C—S = 1.81 (2) Å. The 1,3-distances were set as follows: C···S and C···C in the methylsulfinyl fragment to 2.75 (2) Å, and to 2.52 (2) Å in the remainder of the disordered fragment; C···N to 2.47 (2) Å; C···O(carbonyl) to 2.39 (2) Å; C···O(hydroxy) to 2.58 (2) Å; C···O(sulfoxide) to 2.66 Å.

In order to evaluate whether the stereoselelectivity was maintained across the crystalline bulk, we performed a data collection and an X-ray analysis for another crystal selected from the same sample. For the second data set, the obtained ratio of S_M,R_S:R_M,S_S:S_M,S_S:R_M,R_S stereoisomers was 70:70:30:30. The ^{1}H NMR spectrum does not provide any evidence of the presence of diastereoisomers in solution.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2007); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2007); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS86* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *Stereochemical Workstation Operation Manual* (Siemens, 1989) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3231). Services for accessing these data are described at the back of the journal.

References

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1575.
Bondi, A. (1964). *J. Phys. Chem.* **68**, 441–452.
Bourosh, P., Bologa, O., Simonov, Y., Gerbeleu, N., Lipkowski, J. & Gdaniec, M. (2007). *Inorg. Chim. Acta*, **360**, 3250–3254.
Bruhn, C., Gravenhorst, O., Wagner, C. & Steinborn, D. (1999). *Acta Cryst.* C**55**, 1255–1257.
Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M., Macrae, C. F., McCabe, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst.* B**58**, 389–397.
Freeman, W. A. (1977). *Acta Cryst.* B**33**, 191–194.
Hoshi, T. & Heinemann, H. (2001). *J. Physiol.* **531**, 1–11.
Isab, A. A. & Sadler, P. J. (1977). *Biochim. Biophys. Acta*, **492**, 322–330.
Ivanova, B. B. & Mitewa, M. I. (2004). *J. Coord. Chem.* **57**, 217–221.
Ling, E. C. H., Allen, G. W. & Hambley, T. W. (1993). *J. Chem. Soc. Dalton Trans.* pp. 3705–3710.
Natile, G., Bordignon, E. & Cattalini, L. (1976). *Inorg. Chem.* **15**, 246–248.
Oxford Diffraction (2007). *CrysAlis CCD* and *CrysAlis RED*, including *ABSPACK*. Oxford Diffraction Ltd, Abingdon, Oxfordshire, England.
Schimansky, A., Freisinger, E., Erxleben, A. & Lippert, B. (1998). *Inorg. Chim. Acta*, **283**, 223–232.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Siemens (1989). *Stereochemical Workstation Operation Manual*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Vujačić, A. V., Savić, J. Z., Sovilj, S. P., Szécsényi, M. K., Todorović, N., Petković, M. Ž. & Vasić, V. M. (2009). *Polyhedron*, **28**, 593–599.
Witkiewicz, P. L. & Shaw, C. F. III (1981). *J. Chem. Soc. Chem. Commun.* pp. 1111–1112.