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The absolute configuration of an intermediate cyclic sulfoximine in the asymmetric synthesis of transition-state analog inhibitors of γ-glutamylcysteine synthetase

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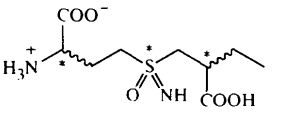
Abstract

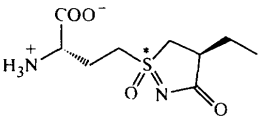
The crystal structure of a cyclic sulfoximine, 2-amino-4-(4-ethyl-1,3-dioxo-4,5-dihydro-1,2-thiazol-1-yl)butanoic acid, $C_9H_{16}N_2O_4S$, was determined to ascertain its stereochemistry. The absolute configuration of the chiral S atom was *S* on the basis of the (*S*)-α-carbon derived from the synthetic precursor, L-homocysteine.

Comment

We demonstrated that sulfoximine derivative (1), a rationally designed transition-state analog, served as



(1)



(2)

an extremely potent mechanism-based inactivator of γ-glutamylcysteine synthetase (γ-GCS, EC 6.3.2.2) (Katoh *et al.*, 1996). This compound, however, was composed of eight possible stereoisomers with respect to two chiral C and one chiral S atom. The inhibition of γ-GCS was reported to be highly dependent on the absolute configuration of the chiral S atom for buthionine sulfoximine, a well known inhibitor of γ-GCS (Campbell *et al.*, 1991). The chirality of the sulfoximine S atom was also important in the inhibition of glutamine synthetase, a mechanistically related synthetase, by methionine sulfoximine (Christensen *et al.*, 1969; Manning *et al.*, 1969; Neidle & Rogers, 1970; Meister, 1992). The establishment of the absolute configuration at the sulfoximine S atom not only helps us understand the detailed three-dimensional structure as an essential element for transition-state mimicry, but also provides evidence for the way in which the mechanism-based enzyme inactivation occurs. In the course of our stereoselective synthesis of sulfoximine (1), we separated two diastereomeric cyclic sulfoximines with respect to the chiral S atom, as a key intermediate (Tokutake *et al.*, 1998). We therefore determined the stereochemistry of one of the diastereomers, (2), by X-ray diffraction analysis to elucidate the relationship between the chirality of the S atom and the enzyme inhibitory activity of sulfoximine (1).

Because of the insolubility of cyclic sulfoximine (2) in water, crystals of (2) were obtained from a mixture of 0.5 *N* HCl–EtOH. The elemental analyses and X-ray diffraction analysis, however, showed that the crystals obtained were not of the HCl salt of sulfoximine (2), but of a zwitterionic amino acid. The molecular structure of cyclic sulfoximine (2) is shown in Fig. 1. The results confirmed clearly that the absolute configuration of the chiral S atom was *S*, based on the known chirality of the α-carbon (C2). The torsion angles in the five-membered ring are in the range 3.9 (2)–14.1 (3)°, indicating that the five-membered ring adopts a planar and not a half-chair

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or envelope conformation. X-ray diffraction analyses of non-cyclized sulfoximine derivatives have been reported previously (Christensen *et al.*, 1969; Neidle & Rogers, 1970; Campbell *et al.*, 1991). The observed bond lengths around the S atom were similar to those observed for (2), but the O3—S1—N2 bond angle of (2) was slightly smaller than those of the linear sulfoximine derivatives, due to the formation of the intramolecular five-membered ring.

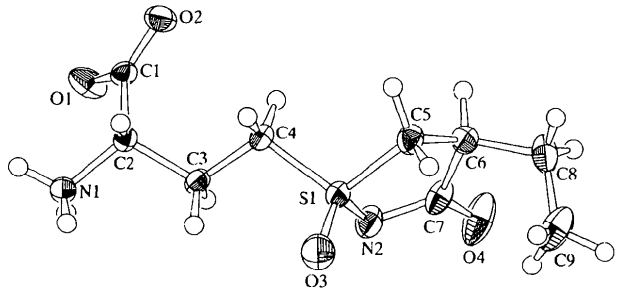

Fig. 1. The molecular structure (*ORTEP*II; Johnson, 1976) of cyclic sulfoximine (2). Displacement ellipsoids are shown at the 50% probability level for non-H atoms.

Experimental

The synthesis of the title compound is reported elsewhere (Tokutake *et al.*, 1998). The crystal used for X-ray crystallographic analysis was obtained by recrystallization from a mixture of 0.5 *N* HCl (5 ml) and EtOH (3 ml) at 277 K.

Crystal data

$C_9H_{16}N_2O_4S$
M_r = 248.30
Monoclinic
$P2_1$
a = 10.545 (1) Å
b = 9.747 (1) Å
c = 5.3893 (5) Å
β = 92.243 (7)°
V = 553.5 (1) Å^3
Z = 2
D_x = 1.490 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 15.1–17.2°
μ = 0.294 mm^{-1}
T = 298.2 K
Block
0.3 × 0.3 × 0.3 mm
Colorless

Data collection

Rigaku AFC-7*R* diffractometer
ω–2θ scans
Absorption correction: none
3418 measured reflections
1709 independent reflections
1649 reflections with $F^2 > 2\sigma(F^2)$

R_{int} = 0.027
θ_{max} = 30°
h = −14 → 14
k = 0 → 13
l = −7 → 7
3 standard reflections
every 150 reflections
intensity decay: 0.30%

Refinement

Refinement on F^2
$R(F)$ = 0.029
$wR(F^2)$ = 0.084
S = 1.033
1709 reflections
144 parameters
H atoms not refined
$w = 1/[\sigma^2(F_o^2) + 0.00422(F_o^2)^2]$

$(\Delta/\sigma)_{max}$ = 0.0008
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

S1—O3	1.441 (1)	S1—C4	1.780 (2)
S1—N2	1.577 (2)	S1—C5	1.775 (2)
O3—S1—N2	114.9 (1)	C4—S1—C5	107.64 (9)
O3—S1—C4	109.40 (8)	S1—N2—C7	110.2 (1)
O3—S1—C5	113.4 (1)	S1—C5—C6	103.4 (1)
N2—S1—C4	109.08 (10)	C5—C6—C7	107.4 (2)
N2—S1—C5	101.97 (8)	N2—C7—C6	115.5 (2)
S1—N2—C7—C6	−11.2 (2)	N2—C7—C6—C5	14.1 (3)
S1—C5—C6—C7	−9.9 (2)	C5—S1—N2—C7	3.9 (2)
N2—S1—C5—C6	4.1 (1)		

Data collection: *Rigaku/AFC Diffractometer Control Software* (Rigaku Corporation, 1998). Cell refinement: *Rigaku/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation/Rigaku Corporation, 1998). Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *TEXSAN*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: OA1081). Services for accessing these data are described at the back of the journal.

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