

Crystal Structure and Molecular Conformation of E-64, a Cysteine Protease Inhibitor

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In order to elucidate the conformational characteristics of cysteine protease inhibitors contributing to their inhibitory activities, the conformation of E-64 (*N*-[*N*-(1-3-*trans*-carboxyoxiran-2-carbonyl)-L-leucyl]-agmatine), a potent inhibitor of papain, was determined by X-ray crystal structure analysis. The molecules were packed in the crystal through electrostatic forces and hydrogen bonding between the oppositely charged terminal groups and between the amide groups. Two crystallographically independent E-64 molecules both took a flattened and slightly curved structure, which is similar to that of loxistatin, a related cysteine protease inhibitor. Based on the present results, a possible inhibitory mechanism of E-64 is proposed, with reference to the binding mode observed in the crystal structure of papain–substrate analogue complex.

Keywords E-64; cysteine protease inhibitor; X-ray crystal analysis; molecular conformation; crystal packing; binding mode

Cysteine proteases containing a highly reactive cysteine residue at the active site have been known as playing important roles in the degeneration of muscular protein,^{1–4)} and in the immunopharmacological response.⁵⁾ For the purposes of studying these biochemical phenomena and treating related diseases, some specific and selective cysteine protease inhibitors have been developed. E-64 (**1**), isolated from the culture of *Aspergillus japonicus* TPR-64,⁶⁾ is one of the most potent inhibitors. The chemical structure of **1** was determined by Hanada *et al.*, as *N*-[*N*-(1-3-*trans*-carboxyoxiran-2-carbonyl)-L-leucyl]-agmatine.⁷⁾ From subsequent exhaustive studies on the structure–activity relationship,^{8–11)} loxistatin (**2**) was designed as a clinical

drug usable for the treatment of muscular dystrophy^{12,13)}; the active form of **2** is E-64-c (**3**).¹⁴⁾ Chemical structures of E-64, loxistatin and E-64-c are shown in Fig. 1(a). The E-64 (**1**) molecule consists of three components, *i.e.*, epoxysuccinyl, leucyl and agmatine moieties, and its terminal carboxyl and guanidyl groups have the negative and positive charges, respectively.

As part of a series of structural studies on the cysteine protease inhibitors, we previously reported the crystal structure of loxistatin,¹⁵⁾ in which the molecular conformation took a “flattened and curved structure” similar to that of *N*-benzyloxycarbonyl phenylalanyl alanine chloromethyl ketone (ZPACK), a substrate analogue covalently binding to the active site of papain (see Fig. 1(b)).¹⁶⁾ Since it has been reported that E-64 has more potent papain inhibitory activity than E-64-c,^{10,11)} we believe that the agmatine moiety of E-64 makes a large contribution to the binding with the active site of papain. This paper deals with the X-ray crystal structure analysis of E-64 to elucidate the conformational characteristics, and the possible binding mode with papain is also discussed.

Results and Discussion

Molecular Conformation The crystallographic data obtained are as follows; $2C_{15}H_{27}N_5O_5 \cdot 4H_2O$, $M_r = 786.9$, triclinic, space group $P1$, $a = 16.535(3) \text{ \AA}$, $b = 12.622(3) \text{ \AA}$, $c = 4.848(1) \text{ \AA}$, $\alpha = 94.03(2)^\circ$, $\beta = 95.54(2)^\circ$, $\gamma = 87.39(2)^\circ$, volume = $1004(1) \text{ \AA}^3$, $D_m = 1.298(1) \text{ g cm}^{-3}$, $D_c = 1.302 \text{ g cm}^{-3}$, $Z = 1$, $\mu(\text{CuK}\alpha) = 8.30 \text{ cm}^{-1}$, $F(000) = 424$. There were two molecules of E-64 (named forms A and B) and four water molecules (named O1W, O2W, O3W and O4W) in a unit cell. Atomic numbering of the E-64 molecule used in this study is shown in Fig. 1(a), and the atomic parameters of nonhydrogen atoms are listed in Table I. High thermal vibration was observed at one atom (C24B), because of its high temperature factors. A stereoscopic (ORTEP¹⁷⁾) drawing of each form is shown in Fig. 2, and the selected torsion angles are listed in Table II.

Forms A and B show very similar conformations except for the C11–C12–C13–C14 carbon chain. Each molecule forms a large plane, and the maximum shift values of atomic coordinates from each best-fit plane are $2.261(5) \text{ \AA}$ (O9A) for form A and $2.127(5) \text{ \AA}$ (O9B) for form

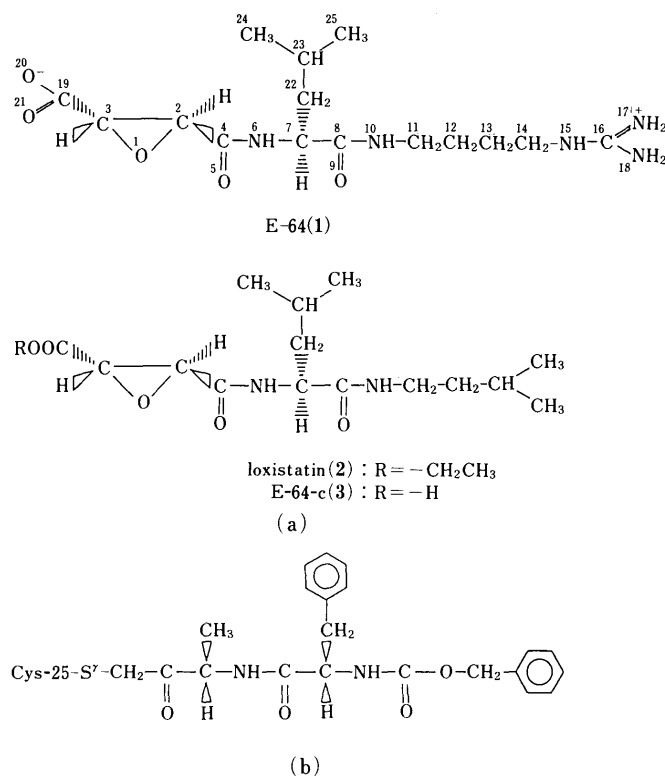


Fig. 1. Chemical Structures of E-64 Analogues (a) and *N*-Benzyloxycarbonylphenylalanylalanine Chloromethyl Ketone (ZPACK) Bound to Cys-25 of Papain (b)

TABLE I. Atomic Coordinates and Isotropic Temperature Factors of Nonhydrogen Atoms with Their Estimated Standard Deviations in Parentheses

Atom ^{a)}	x	y	z	B _{eq}
O1A	0.2585 (3)	0.6337 (4)	-0.270 (1)	4.9 (2)
C2A	0.3223 (3)	0.5809 (4)	-0.098 (1)	3.5 (2)
C3A	0.2521 (4)	0.5264 (6)	-0.231 (1)	4.4 (2)
C4A	0.4038 (3)	0.5709 (4)	-0.215 (1)	3.0 (2)
O5A	0.4078 (3)	0.5755 (4)	-0.4682 (8)	4.2 (2)
N6A	0.4655 (3)	0.5577 (3)	-0.0319 (8)	3.2 (1)
C7A	0.5490 (3)	0.5566 (4)	-0.1062 (9)	3.1 (2)
C8A	0.5989 (3)	0.4620 (3)	0.0130 (9)	2.8 (2)
O9A	0.6014 (3)	0.4484 (3)	0.2642 (8)	4.0 (1)
N10A	0.6387 (3)	0.4012 (3)	-0.1666 (8)	3.2 (1)
C11A	0.6956 (3)	0.3159 (4)	-0.078 (1)	3.8 (2)
C12A	0.7630 (4)	0.2981 (4)	-0.272 (1)	3.6 (2)
C13A	0.8138 (4)	0.3961 (4)	-0.287 (1)	3.9 (2)
C14A	0.8841 (4)	0.3720 (4)	-0.462 (1)	3.8 (2)
N15A	0.9262 (3)	0.4696 (4)	-0.481 (1)	4.3 (2)
C16A	0.9910 (3)	0.4753 (4)	-0.620 (1)	3.8 (2)
N17A	1.0163 (3)	0.3938 (4)	-0.779 (1)	4.4 (2)
N18A	1.0272 (4)	0.5654 (5)	-0.609 (2)	5.9 (3)
C19A	0.1854 (4)	0.5000 (6)	-0.053 (1)	4.7 (3)
O20A	0.1568 (3)	0.5747 (5)	0.088 (1)	6.1 (2)
C21A	0.1691 (4)	0.4049 (5)	-0.050 (2)	7.1 (3)
C22A	0.5886 (4)	0.6610 (4)	-0.001 (1)	3.9 (2)
C23A	0.6754 (4)	0.6738 (4)	-0.076 (1)	4.1 (2)
C24A	0.7404 (4)	0.6320 (6)	0.137 (2)	5.1 (3)
C25A	0.6904 (5)	0.7908 (5)	-0.127 (3)	6.8 (4)
O1B	0.8520 (3)	0.0696 (3)	0.486 (1)	4.6 (2)
C2B	0.7841 (3)	0.0309 (4)	0.320 (1)	3.1 (2)
C3B	0.8469 (3)	-0.0422 (4)	0.440 (1)	3.5 (2)
C4B	0.7033 (3)	0.0443 (4)	0.439 (1)	3.0 (2)
O5B	0.6982 (3)	0.0486 (4)	0.6872 (8)	4.3 (2)
N6B	0.6381 (3)	0.0525 (4)	0.2507 (9)	3.8 (2)
C7B	0.5540 (4)	0.0686 (5)	0.321 (1)	4.1 (2)
C8B	0.5059 (3)	-0.0273 (5)	0.213 (1)	3.6 (2)
O9B	0.4985 (3)	-0.0529 (4)	-0.0389 (8)	5.0 (2)
N10B	0.4747 (3)	-0.0797 (4)	0.3969 (9)	3.9 (2)
C11B	0.4242 (4)	-0.1706 (5)	0.336 (2)	5.3 (3)
C12B	0.3314 (6)	-0.143 (1)	0.309 (3)	7.9 (5)
C13B	0.3083 (8)	-0.076 (1)	0.572 (3)	8.6 (6)
C14B	0.2140 (8)	-0.0609 (9)	0.552 (3)	7.8 (5)
N15B	0.1794 (4)	-0.1547 (5)	0.660 (2)	5.6 (3)
C16B	0.1107 (4)	-0.1460 (6)	0.791 (1)	4.7 (2)
N17B	0.0687 (4)	-0.0581 (6)	0.793 (1)	5.8 (3)
N18B	0.0911 (4)	-0.2261 (6)	0.927 (2)	6.3 (3)
C19B	0.9060 (4)	-0.0954 (4)	0.250 (1)	3.9 (2)
O20B	0.9215 (3)	-0.1926 (4)	0.267 (1)	5.1 (2)
C21B	0.9338 (3)	-0.0385 (4)	0.086 (1)	5.4 (2)
C22B	0.5164 (4)	0.1728 (6)	0.214 (2)	5.8 (3)
C23B	0.4298 (5)	0.1984 (6)	0.300 (3)	6.7 (4)
C24B	0.417 (1)	0.313 (1)	0.367 (8)	16. (2)
C25B	0.3660 (6)	0.151 (1)	0.124 (3)	8.1 (5)
O1W	0.9046 (4)	0.6893 (4)	0.724 (1)	5.7 (2)
O2W	0.0595 (5)	0.1437 (6)	0.571 (2)	7.5 (3)
O3W	0.9657 (5)	0.1765 (4)	0.053 (1)	6.4 (3)
O4W	0.1938 (5)	0.2644 (7)	0.492 (2)	8.5 (4)

$$B_{eq} = 4/3 (B_{11}a^2 + B_{22}b^2 + B_{33}c^2 + 2B_{12}ab \cos \gamma + 2B_{13}ac \cos \beta + 2B_{23}bc \cos \alpha).$$

a) The suffix letters A and B represent forms A and B of 1, respectively.

B respectively. E-64 has three asymmetric carbon atoms (C2, C3 and C7) in a molecule, and all of them take the *S* configuration. The epoxy ring takes the dihedral angles of 99.6(8)° and 77.0(6)° respectively with the neighboring carboxyl (C19, O20 and O21 atoms) and amide (C4, O5 and N6 atoms) planes for form A, and 96.6(7)° and 82.6(6)° for form B. The carboxyl and amide groups are *trans* connected to the epoxy ring with respect to

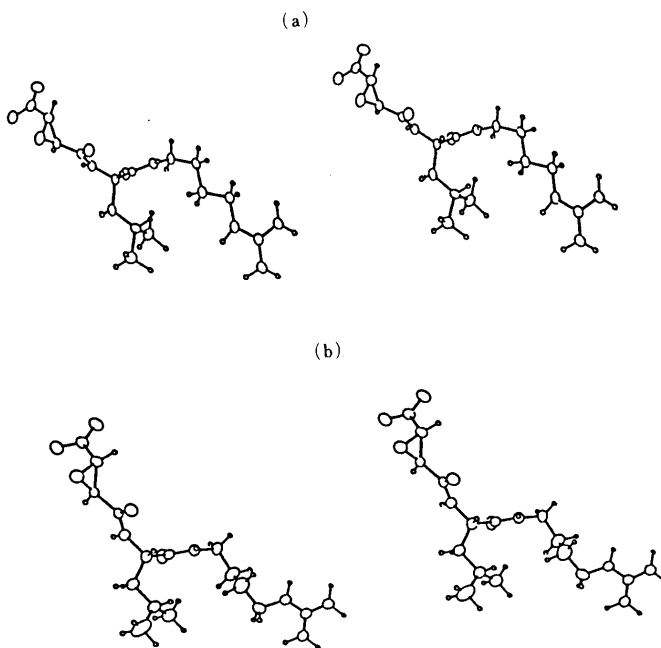


Fig. 2. Stereoscopic Drawings of the Two Crystallographically Independent Molecules of 1

(a) Form A. (b) Form B. The thermal ellipsoid of nonhydrogen atom is expressed with 50% probability.

TABLE II. Selected Torsion Angles of 1 Observed in Forms A and B with Estimated Standard Deviations in Parentheses

Bond	Angle (°)	
	Form A	Form B
O1-C2-C3-C19	-105.3 (7)	-104.4 (6)
C4-C2-C3-C19	154.1 (7)	150.1 (5)
O1-C3-C19-O20	-16.0 (6)	-22.7 (5)
O1-C3-C19-O21	168.5 (8)	158.9 (6)
C2-C3-C19-O21	53.9 (6)	43.4 (5)
C2-C3-C19-O21	-121.6 (7)	-135.0 (6)
O1-C2-C4-O5	-21.9 (5)	-27.7 (5)
O1-C2-C4-N6	158.0 (5)	151.5 (5)
C3-C2-C4-O5	43.7 (5)	40.8 (5)
C3-C2-C4-N6	-136.3 (5)	-140.1 (5)
C2-C4-N6-C7; ω_1	-174.1 (5)	-178.4 (6)
O5-C4-N6-C7	5.8 (4)	0.7 (5)
C4-N6-C7-C8; ϕ_1	-132.6 (5)	-115.5 (5)
C4-N6-C7-C22	105.1 (5)	119.2 (6)
N6-C7-C8-O9	-53.5 (5)	-60.5 (6)
N6-C7-C8-N10; ψ_1	128.1 (4)	118.9 (5)
C22-C7-C8-O9	68.8 (5)	63.5 (6)
C22-C7-C8-N10	-109.6 (5)	-117.2 (6)
N6-C7-C22-C23; χ^{11}	-177.1 (5)	-175.8 (7)
C8-C7-C22-C23	60.3 (5)	60.8 (7)
C7-C22-C23-C24; χ^{21}	-89.4 (5)	-85.2 (9)
C7-C8-N10-C11; ω_2	173.0 (5)	177.5 (7)
O9-C8-N10-C11	-5.3 (4)	-3.2 (6)
C8-N10-C11-C12; ϕ_2	-149.9 (5)	-93.5 (8)
N10-C11-C12-C13	60.0 (5)	-53.8 (8)
C11-C12-C13-C14	175.2 (5)	-174. (1)
C12-C13-C14-N15	176.7 (5)	84.9 (9)
C13-C14-N15-C16	179.9 (6)	147.6 (9)
C14-N15-C16-N17	7.7 (5)	8.9 (8)
C14-N15-C16-N18	-175.9 (7)	-167.4 (9)

each other, and the torsion angles of C19-C3-C2-C4 are 154.1(7)° for form A and 150.1(5)° for form B. The common conformation can further be seen in the orien-

tation of two keto groups with respect to the epoxy ring; the torsion angles of C2–C3–C19–O20 and C3–C2–C4–O5 are $53.9(6)^\circ$ and $43.7(5)^\circ$ for form A and $43.4(5)^\circ$ and $40.8(5)^\circ$ for form B; each C=O bond has a (*gauche*, *gauche*) orientation to the ring. These conformational features have also been observed in the loxistatin crystal¹⁵ and they would be a characteristic of *trans* epoxysuccinyl compounds which stereochemically contribute to the inhibitory activity.⁹⁾

The two peptide groups are all *trans* and are nearly planar with $\omega_1 = -174.1(5)^\circ$ and $\omega_2 = 173.0(5)^\circ$ for form A and $\omega_1 = -178.4(6)^\circ$ and $\omega_2 = 177.5(7)^\circ$ for form B. The (ϕ_1, ψ_1) angles are both in a β -sheet region of the Ramachandran plot¹⁸⁾ and thus the two main chains around both leucine residues could be in a stable conformation. Similar conformation between both forms is also seen in the leucyl side chain; the torsion angles around both leucine residues take a commonly stable conformation, as observed in loxistatin and the majority of L-leucine structures.¹⁹⁾ The ϕ_2 angles are both in the (*-anti-clinal*) region, although their significant difference appears to result from the interaction of the agmatine moieties with neighboring

molecules.

In the *n*-butyl group of the agmatine moiety, we can see a large conformational difference between forms A and B. While the torsion angles about the C11–C12–C13–C14

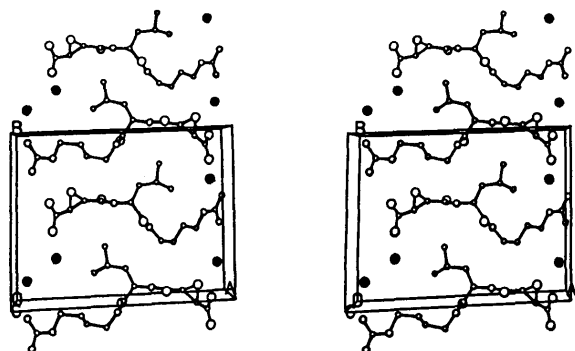


Fig. 3. Stereoscopic Drawing of Molecular Packing of 1 Viewed along the *c*-Axis

Water molecules are expressed with closed circles.

TABLE III. Distances and Angles around Hydrogen Bonds of 1 with Their Estimated Standard Deviations in Parentheses

Donor (D)	Acceptor (A)	Distance (Å)		Angle (°)
		D...A	H...A	
N6A	O5A ^{a)}	2.971 (6)	2.07 (9)	166 (8)
N6B	O5B ^{b)}	2.993 (6)	2.08 (9)	163 (8)
N10A	O9A ^{b)}	2.867 (6)	1.89 (9)	170 (8)
N10B	O9B ^{a)}	2.725 (7)	1.82 (9)	154 (8)
N15A	O1W ^{b)}	2.989 (8)	2.0 (1)	162 (9)
N15B	O1A ^{c)}	2.946 (8)	1.9 (1)	161 (9)
N17A	O21A ^{d)}	2.971 (9)	2.10 (8)	173 (8)
	O3W ^{b)}	2.941 (8)	2.0 (1)	159 (9)
N17B	O20B ^{e)}	2.751 (9)	1.7 (1)	169 (9)
	O2W	2.82 (1)	2.0 (1)	140 (10)
N18A	O20A ^{d)}	2.723 (9)	1.9 (1)	176 (9)
	O1W ^{b)}	3.026 (9)	2.1 (1)	150 (10)
N18B	O21B ^{e)}	3.385 (9)	2.3 (2)	180 (10)
	O20A ^{c)}	2.82 (1)	1.88 (8)	153 (7)
O1W	O20B ^{f)}	2.798 (7)		
O3W	O21B	2.806 (8)		
O4W	O21A ^{a)}	2.79 (1)		

a–f) Denote the following equivalent positions relative to the donor molecules at *x, y, z*: a) *x, y, z* + 1; b) *x, y, z* – 1; c) *x, y* – 1, *z* + 1; d) *x* + 1, *y, z* – 1; e) *x* – 1, *y, z* + 1; f) *x, y* + 1, *z* + 1.

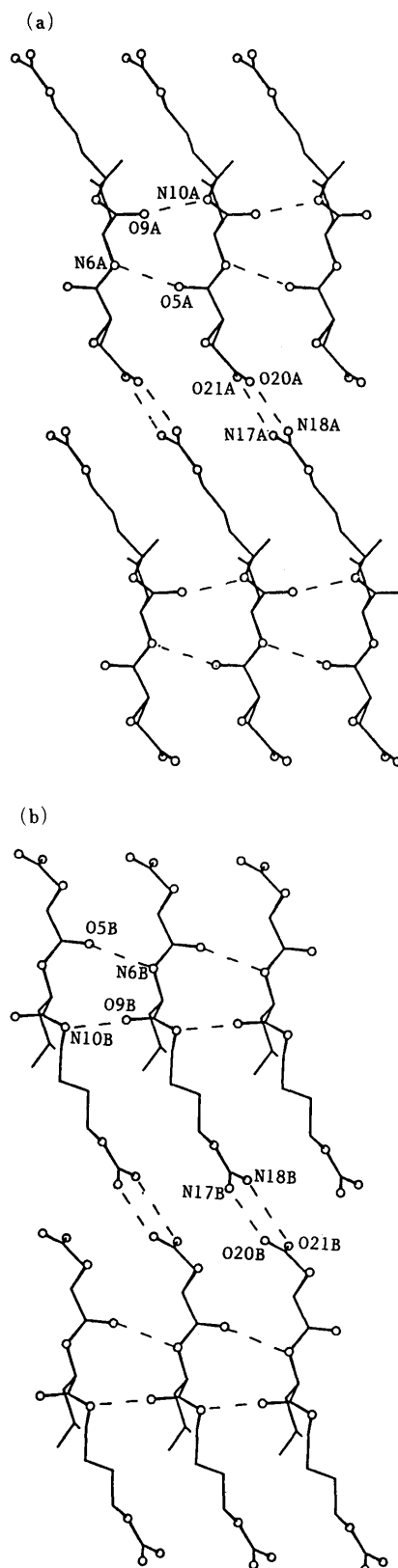


Fig. 4. Perspective Drawings of the Molecular Packings of Forms A (a) and B (b), Viewed along the *b*-Axis

Nitrogen and oxygen atoms are represented by spheres.

carbon chain take all-*trans* conformations for form A, those of form B are significantly distorted; the guanidyl group of form B is connected to the leucyl residue with the markedly twisted torsion angles. Thus, form A itself seems to be conformationally more stable than form B. However the latter distorted conformation would be convenient for forming hydrogen bonds between the guanidyl group and neighboring molecules (discussed later). The guanidyl group is planar and the guanidyl plane (N15, C16, N17 and N18 atoms) takes a dihedral angle of $-14.4(8)^\circ$ with respect to the carboxyl plane (C19, O20 and O21 atoms) for form A and $161.5(8)^\circ$ for form B.

Overall, both conformations of forms A and B could be described as flattened and slightly curved. Compared with the conformation of loxistatin, however, these conformations are more extended, presumably because of stretching owing to the zwitterionic character of E-64.

Crystal Packing and Hydrogen Bonds The crystal packing viewed along the *c*-axis is shown in Fig. 3. Two independent E-64 molecules in a unit cell were packed to each other with an orientation nearly parallel to the *b*-axis. Because the respective terminal carboxyl and guanidyl groups are charged oppositely, the neighboring molecules along the *a*- and *b*-axes would be attracted to each other through the electrostatic forces.

Hydrogen bond distances and angles are listed in Table III, and the binding modes for forms A and B, viewed along the *b*-axis, are shown in Fig. 4(a) and (b). Two kinds of hydrogen bond pairs are formed; one is formed between the terminal charged groups in a head-to-tail fashion, and the other is formed between two neighboring peptide groups characterized as parallel β -sheet structure.²⁰⁾ Both hydrogen bond pairs connect the respective molecules of forms A and B. The water molecules (O1W—O4W) stabilize the molecular packings of forms A and B via hydrogen bond formations (see Table III). No significant hydrophobic interaction was observed in this crystal.

Biochemical Implications of E-64 Conformation Among cysteine proteases, papain,²¹⁾ actinidin²²⁾ and calotropic

DI²³⁾ have been subjected to protein crystallographic analyses, and these enzymes were shown to have structural similarity to one another. Thus, the possible binding of E-64 with one of them should apply equally for the other cysteine proteases. Fortunately, the binding mode of papain-ZPACK complex¹⁶⁾ has been elucidated by the X-ray diffraction method (see Fig. 1 for the chemical structure of ZPACK). In the binding mode shown in Fig. 5(a), two benzyl groups of ZPACK are positioned at the two hydrophobic holes of the papain active site; one is mainly formed by the side chains of Val-133 and Val-157, the other by those of Tyr-61 and Tyr-67. It is worthwhile to note that the loxistatin¹⁵⁾ and E-64 molecules take conformations similar to that of ZPACK, that is to say, flattened and curved (compare Fig. 5(a) with (b) and (c)). If the leucyl side chain and the isoamylamide group (loxistatin) or agmatine moiety (E-64) are respectively fitted to the phenylalanyl side chain and the benzyloxycarbonyl group of ZPACK, the epoxy ring and the terminal carboxyl group will be positioned in the vicinity of the S^γ atom of Cys-25 and N^{δ1} atom of His-159, respectively. In fact, it was recently suggested that the C3 atom of the E-64 epoxy ring binds to the S^γ atom and forms an irreversible thioether bond.²⁴⁾ The charged carboxyl and guanidyl (for E-64) groups could be stabilized by hydrogen bonds and/or electrostatic interaction with the neighboring polar amino acid residues. For example, the distance between the terminal charged groups of the E-64 molecule is about 15 Å in the crystal structure, and the distance between the N^{δ1} atom of His-159 and the O^γ atom of Tyr-61 is 15.4 Å in the papain-ZPACK complex. Thus, the E-64 molecule can form hydrogen bonds with these atoms. It appears important to note in connection with this possible binding mode (see Fig. 6) that the potent inhibitory activity of E-64 characterized by the guanidyl group could be explained by the tight interactions of this group with the papain active site, especially with Tyr-61 and Tyr-67 residues, and that the protonated imidazole ring of His-159, which is important for the normal catalytic action of papain,²⁵⁾ is po-

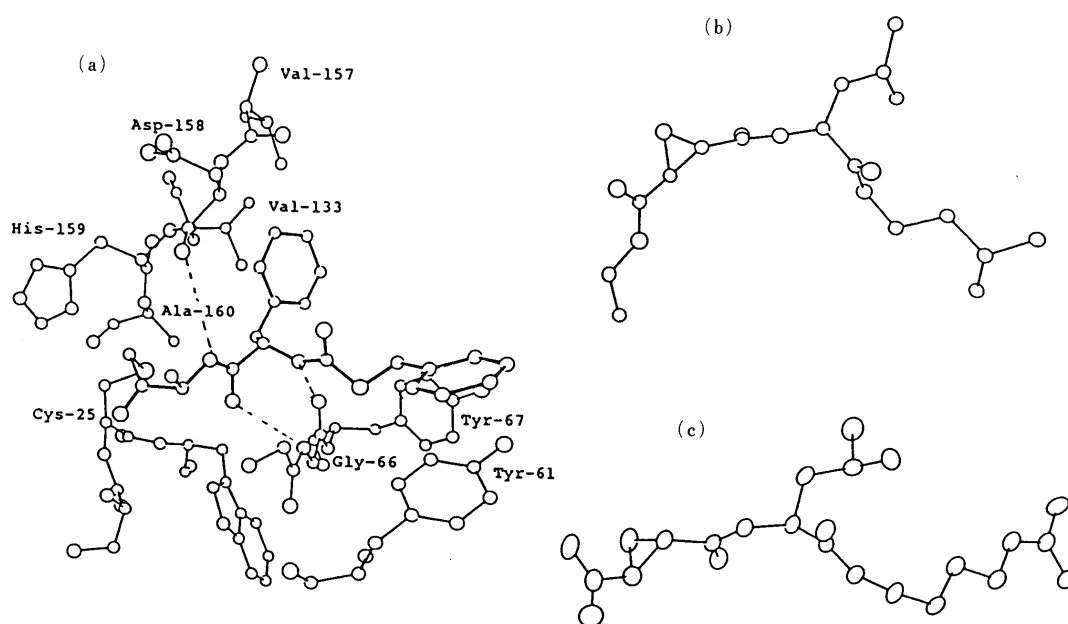


Fig. 5. Conformational Comparison of ZPACK Bound to Papain (a) with Loxistatin (b) and E-64 (c) Observed in the Crystal Structures

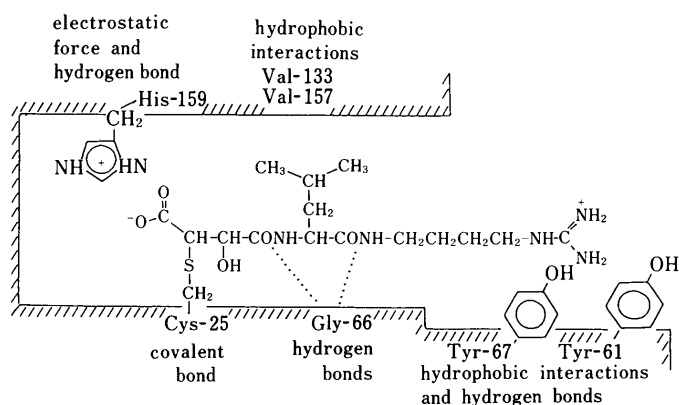


Fig. 6. Possible Binding Mode between E-64 and Papain

sitioned at a location which permits hydrogen-bond formation with the terminal carboxyl group of the E-64 molecule. Furthermore, hydrogen bonds could be formed between Gly-66 of papain and the two peptide groups of E-64, characterized as parallel β -sheet structure.

In summary, we have determined the molecular conformation of E-64 by X-ray crystal analysis. Based on the results, a possible binding mode between E-64 and papain is proposed. The nonbonded interactions which would be important for the binding of E-64 with the active site of papain were also observed in the crystal packing of the E-64 crystal.

Experimental

Crystallization of 1 and Data Collection Compound 1 was purchased from Peptide Institute Inc. Transparent needle crystals were finely obtained by slow evaporation of the $\text{H}_2\text{O}-\text{C}_2\text{H}_5\text{O}-(\text{CH}_3)_2\text{CHOH}$ (1:2:2) mixture at room temperature. The crystal density was measured by the flotation method in CCl_4 -benzene mixture.

A single crystal ($0.3 \times 0.2 \times 0.2$ mm) was mounted on a Rigaku automated four-circle diffractometer. Using graphite-monochromated $\text{CuK}\alpha_1$ radiation ($\lambda = 1.5405$ Å), the unit cell dimensions were determined by least-squares calculation with 2θ values of 25 high-angle reflections.

Intensity data of 3275 independent reflections [$F_0 > 3\sigma(F_0)$] within $2\theta = 130^\circ$ were obtained using the ω - 2θ scan technique. The scan speed was $4^\circ/\text{min}$; the background was measured for 5 s. Corrections were applied for Lorentz and polarization factors, but not for absorption effects.

Solution and Refinement of the Crystal Structure of 1 The crystal structure of 1 was solved by the direct method (MULTAN84²⁶) program. An electron density map was computed with a phase set having the highest figure of merit using 400 reflections with the normalized structure factors $|E| > 1.51$. This map gave the positions of 19 nonhydrogen atoms in an asymmetric unit. Reasonable positions for remaining nonhydrogen atoms were determined by successive Fourier syntheses. Using 3253 reflections [$F_0 > 4\sigma(F_0)$], the atomic parameters were refined by the block-diagonal least-squares method with anisotropic temperature factors for the nonhydrogen atoms and isotropic ones for the hydrogen atoms. $\sum w(|F_0| - |F_C|)^2$ was minimized, where w represents the weight for refinement and was used in the last stage as follows: $w = 1.0/[\sigma(F_0)^2 - 0.02581|F_0| + 0.01586|F_0|^2]$. The discrepancy indexes $R = [\sum ||F_0| - |F_C|| / \sum |F_0|]$ and $R_w = [\sum w(|F_0| - |F_C|)^2 / \sum w|F_0|^2]^{1/2}$ were 0.093 and 0.104, respectively; and S (goodness of fit) $= [\sum w(|F_0| - |F_C|)^2 / (M - N)]^{1/2}$, M = number of observed reflections and N = number of variables was 1.43. Maximum and minimum electron densities in the final difference Fourier syntheses were $0.34 \text{ e}\text{\AA}^{-3}$ and $-0.23 \text{ e}\text{\AA}^{-3}$, respectively.

All numerical calculations were performed using the UNICS²⁷) pro-

grams. Atomic scattering factors summarized in the 'International Tables for X-Ray Crystallography'²⁸) were used. All computations were carried out on the DEC MicroVAX-II computer system at the Computing Center, Osaka University of Pharmaceutical Sciences. Tables of observed and calculated structure factors, anisotropic temperature factors of nonhydrogen atoms and atomic parameters of hydrogen atoms are available from one of authors (D.Y.) on request.

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