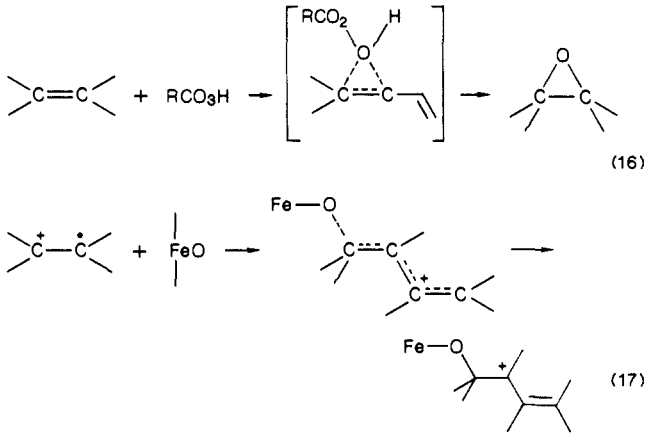
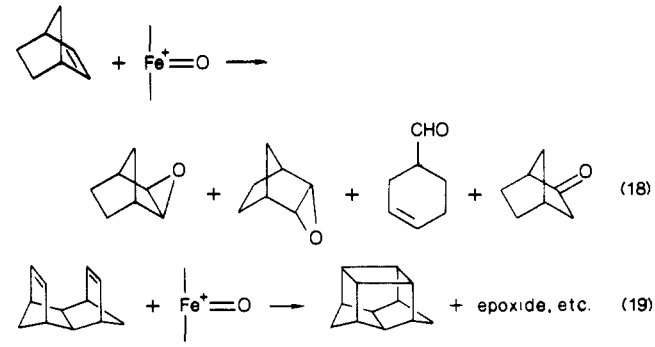


intervention are the skeletal rearrangements (eq 18) and cation radical type alkene rearrangements (eq 19) that accompany hemin-catalyzed epoxidation.[8,9,44,45]

The electron-transfer mechanism shown in Scheme I seems to be consistent with these results and with rates of reactions of simple reactive alkenes with high-valent iron porphyrins.

It is not as yet clear whether such an electron-transfer process extends to other less reactive alkenes such as, e.g., acrylic esters, or to other metalloporphyrin catalysts, e.g., Mn and Cr, where



different reactivities are seen.[35,46,47] These questions are under investigation.

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Registry No. 1, 111-66-0; **2**, 762-62-9; **3**, 100-42-5; **4**, 622-97-9; **5**, 762-72-1; **6**, 127-91-3; **7**, 1192-37-6; **8**, 110-83-8; **9**, 931-87-3; **10**, 498-66-8; **11**, 627-20-3; **12**, 7642-04-8; **13**, 645-49-8; **14**, 1501-82-2; **15**, 4050-45-7; **16**, 873-66-5; **17**, 103-30-0; **18**, 80-56-8; **19**, 563-79-1; **20**, 1076-13-7; **21**, 5194-50-3; **22**, 538-81-8; **23**, 7235-40-7; **24**, 67-56-1; I, 91042-27-2; PFIB, 14353-90-3; MCPBA, 937-14-4; cytochrome P-450, 9035-51-2.

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Cyclic Cystine Peptides. Antiparallel β-Sheet Conformation for the 20-Membered Ring in Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe (S—S)

Isabella L. Karle,* R. Kishore,† S. Raghothama,‡ and P. Balaram†

Contribution from the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375-5000, and Molecular Biophysics Unit and Sophisticated Instruments Facility, Indian Institute of Science, Bangalore 560 012, India. *Received July 20, 1987*

Abstract: Crystal structure analysis of a synthetic cystine peptide, Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe, containing a S–S 20-membered ring, establishes for the first time in the solid state an antiparallel β-sheet conformation for a peptide molecule with a –S–S– bridge. The antiparallel β-sheet of an individual molecule is extended to the whole crystal by intermolecular hydrogen bonding. A type II′ β-bend reversal is formed at Aib[3]-Ala[4]. This is the first occurrence of an Aib residue at the $i + 1$ position in a type II or II′ β-bend. Three nearly parallel intramolecular hydrogen bonds have N···O distances of 2.85–2.89 Å. In the disulfide bridge $C^{\alpha}(1)$–$C^{\beta}(1)$–S(1)–S(6)–$C^{\beta}(6)$–$C^{\alpha}(1)$, S–S = 2.027 Å, angles $C^{\beta}SS$ = 106.3 and 105.3°, and the torsional angles are −55, −101, +101, −84, and −55°, respectively. The space group is $P2_12_12_1$ with a = 18.674 (3) Å, b = 18.614 (3) Å, and c = 12.652 (3) Å with 1 formula unit $C_{30}H_{53}N_7O_8S_2 \cdot H_2O \cdot (CH_3)_2SO$ per asymmetric unit. Least-squares refinement of 2145 data observed $>3\sigma(F)$ yielded an R factor of 9.6%. Analysis of nuclear Overhauser effect data in $CDCl_3$ and $(CD_3)_2SO$ favors a population of type I′ Aib-Ala β-turn conformation in solution, with the antiparallel β-sheet structure being maintained.

Disulfide cross-links can stabilize specific conformations in model oligopeptides.[1] This report describes the structure of the synthetic cyclic cystine peptide Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe (**1**),[2] in the crystalline S–S state, providing the first example of disulfide bridging across an antiparallel β-sheet and also the first example of an α-aminoisobutyryl residue (Aib) at the $i + 1$ position of a type II′ β-turn. A chain reversal at Aib-Ala and three intramolecular NH···O=C hydrogen bonds result in a pleated antiparallel β-sheet structure. Surveys of crystal structures of globular proteins have not found any disulfide bridges between neighboring strands of β-sheets.[3]

* Laboratory for the Structure of Matter.
† Molecular Biophysics Unit.
‡ Sophisticated Instruments Facility.

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(2) (a) Abbreviations used: Aib, α-aminoisobutyric acid; NOE, nuclear Overhauser effect; Boc, (*tert*-butyloxy)carbonyl. (b) All chiral amino acids are of the L configuration.

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Among oligopeptides containing the -S-S- bond there have been only two reports of crystal structures of peptides with four intervening residues: deaminooxytocin,[4] Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2, and pressinoic acid,[5] Cys-Tyr-Phe-Gln-Asn-Cys. Although the 20-membered rings in both deaminooxytocin and pressinoic acid have several transannular hydrogen bonds, neither ring has any features that resemble a β-sheet. It has been postulated in the literature that disulfide bridges and β-sheets are incompatible.[3b]

Previous to the crystal structure analysis, the conformation of the present compound was examined in solution in $CDCl_3$.[1f] The presence of three intramolecular hydrogen bonds involving the Leu, Val, and methylamide NH groups was established by ^1H NMR studies at 270 MHz. Hydrogen-bonding studies, together with unusually low-field positions of the Cys[1] and Cys[6] $C^\alpha H$ resonances and high $J_{HNC^\alpha H}$ values, provided support for an intramolecular antiparallel β-sheet conformation, facilitated by a chain reversal at the Aib-Ala segment. The present crystal structure analysis confirms the β-sheet conformation in the individual molecules, shows the extension of an approximate antiparallel β-sheet throughout the crystal by means of intermolecular hydrogen bonding, and provides parameters for the pleated sheet, the disulfide bridge, and the chain reversal. The β-bend at Aib-Ala has been established to be type II′ in the crystal, different than the type I′ proposed in solution.[1f] This is the first occurrence of an Aib residue in either a type II or II′ β-turn. Crystallographic studies of a large number of peptides containing Aib residues have not shown any previous examples for such a conformation for an Aib residue located centrally in an oligopeptide.[6-8] Further, nuclear Overhauser effect (NOE) data in $(CD_3)_2SO$, the solvent of crystallization, are presented to facilitate a comparison between solid-state and solution conformations.

Experimental Section

X-ray Diffraction. Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe was synthesized by conventional solution-phase procedures.[1f] Crystals were grown from DMSO. An irregular fragment, roughly a cube of dimensions 0.17–0.20 mm, was cut out of a clump of prisms and mounted in a thin glass capillary in contact with some mother liquor. X-ray diffraction data were measured on an automated four-circle diffractometer using Cu Kα radiation and a graphite monochromator (λ = 1.541 78 Å). The θ–2θ scan technique was used with a 2.0° scan, a variable scan rate up to 15°/min, $2\theta_{max}$ = 115°, and *hkl* ranges from 0 to a maximum of 20, 19, and 13, respectively. The intensities were corrected empirically for a 15% decline in intensity of 3 standard reflections monitored after every 60 measurements. A total of 3112 unique reflections were measured of which 2145 had intensities $>3\sigma(F)$. Lorentz and polarization corrections were applied to the data. The space group is $P2_12_12_1$ with a = 18.674 (3) Å, b = 18.614 (3) Å, c = 12.652 (3) Å, V = 4398 Å^3, and Z = 4. The calculated density is 1.186 g/cm^3 based on a molecular weight of 785.06 for $C_{30}H_{53}N_7O_8S_2 \cdot H_2O \cdot (CH_3)_2SO$.

The structure was solved by direct-phase determination[9] with a computer program.[10] The placement of the oxygen of one water molecule that participates in strong hydrogen bonds with the peptide molecules is well determined. The other solvent molecule is DMSO. Although the O of DMSO participates in one strong hydrogen bond with N(3), the DMSO molecule occurs in a fairly large cavity that permits the pyramidal molecule to assume various positions in the cavity subject to the constraint of the S=O···N(3) hydrogen bond. An approximate description of the disorder for the least-squares refinement required two sites for the S(s) atom (see S(s) and S(s)′ in the table of coordinates) at occupancies of ~0.7 and ~0.3. The closest approaches to atom S(s)′ are atoms C(2) and O(4) at distances greater than 3.75 Å. A similar disorder of DMSO in a large cavity was found in the crystal structure of *cyclo*(L-Leu-L-Tyr-$^\delta$Ava-$^\delta$Ava).[11] The presence of a fairly large disordered solvent molecule usually contributes to a relatively large R factor. Idealized positions for 46 hydrogen atoms occurring on C atoms were included in the least-squares refinement. The R factor was 9.6% for 2145 data observed greater than $3\sigma(F)$. Fractional coordinates for the nonhydrogen atoms are listed in Table I. Bond lengths and angles are shown in Table II, and torsional angles are listed in Table III.

Spectroscopic Studies. Difference NOE studies were carried out at 343 K in $(CD_3)_2SO$ and at 293 K in $CDCl_3$ using a peptide concentration of 10 mg mL^{-1}. All spectra were recorded on a Bruker WH-270 FT-NMR spectrometer as previously described.[1f] All observed NOEs are positive. CD spectra were recorded on a Jasco J-20 spectropolarimeter.

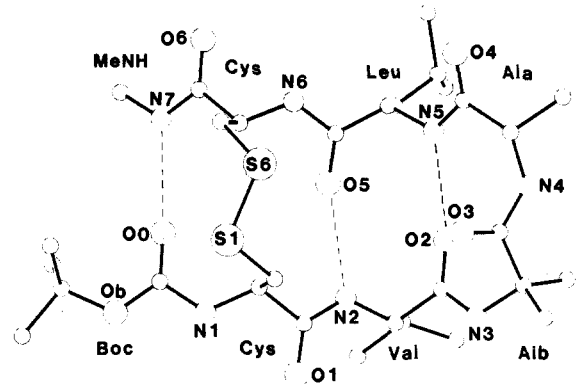

Figure 1. β-Sheet conformation of Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe in the crystal. Intramolecular hydrogen bonds are indicated by dashed lines. The disulfide bridge is flanked on either side by NH···O=C hydrogen bonds.

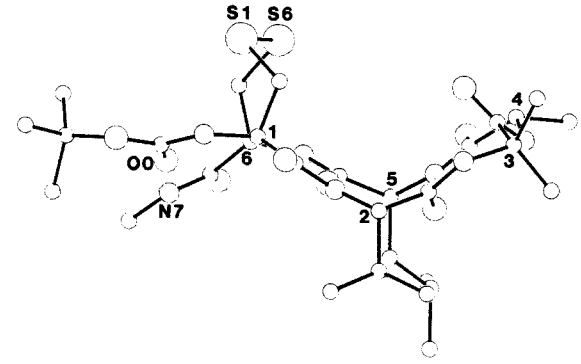

Figure 2. Side view of molecule in Figure 1 showing pleats in backbone and the disulfide bridge from $C^\alpha(1)$ and $C^\alpha(6)$. The C^α atoms are numbered 1–6.

Discussion

Antiparallel β-Sheet. The conformation of the molecule is shown in Figure 1. The backbone undergoes a reversal at residues 3 and 4. Hydrogen bonds between the two antiparallel portions of the chain occur between N(2)H···O(5), N(5)H···O(2), and N(7)H···O(0) with normal lengths (see Table IV). A side view of the molecule (Figure 2) shows the pleating of the backbone that is characteristic of an antiparallel β-sheet. The -S-S- bridge from $C^\beta(1)$ to $C^\beta(6)$ fits comfortably from one β-strand to the

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Table I. Atom Coordinates (×10⁴) and Temperature Factors (Å² × 10³)

atom	x	y	z	U_{eq}[a]
C(4)	8578 (9)	10865 (10)	2598 (17)	146 (11)
C(3)	7675 (11)	10916 (10)	3957 (19)	164 (12)
C(2)	7401 (12)	10264 (13)	2233 (18)	189 (14)
C(1)	7975 (8)	10436 (8)	3063 (16)	98 (7)
Ob	8302 (4)	9817 (5)	3534 (9)	82 (4)
C(0)	7912 (7)	9309 (8)	3991 (12)	71 (6)
O(0)	7281 (5)	9351 (5)	4261 (10)	99 (5)
N(1)	8311 (5)	8706 (6)	4173 (9)	63 (4)
$C^{\alpha}(1)$	8010 (6)	8065 (7)	4625 (12)	65 (5)
C′(1)	8499 (6)	7725 (7)	5450 (11)	59 (5)
O(1)	9159 (4)	7810 (5)	5350 (8)	75 (4)
$C^{\beta}(1)$	7888 (7)	7496 (7)	3777 (12)	77 (6)
S(1)	7353 (2)	7750 (3)	2649 (3)	93 (2)
N(2)	8189 (4)	7385 (5)	6220 (8)	53 (4)
$C^{\alpha}(2)$	8535 (6)	6944 (6)	6986 (10)	47 (4)
C′(2)	8114 (6)	6244 (8)	7013 (11)	60 (5)
O(2)	7476 (4)	6281 (4)	7317 (7)	61 (3)
$C^{\beta}(2)$	8553 (8)	7271 (7)	8091 (12)	74 (6)
$C^{\gamma}(21)$	8981 (7)	7966 (8)	8112 (14)	99 (7)
$C^{\gamma}(22)$	8805 (10)	6795 (10)	8920 (14)	124 (9)
N(3)	8454 (4)	5635 (5)	6765 (8)	46 (3)
$C^{\alpha}(3)$	8067 (6)	4937 (7)	6834 (9)	52 (5)
C′(3)	7353 (7)	5040 (7)	6229 (9)	53 (4)
O(3)	7344 (4)	5265 (5)	5340 (6)	68 (3)
$C^{\beta}(31)$	8011 (6)	4721 (7)	7961 (9)	58 (5)
$C^{\beta}(32)$	8481 (6)	4381 (7)	6204 (11)	68 (5)
N(4)	6755 (5)	4822 (6)	6736 (9)	64 (4)
$C^{\alpha}(4)$	6047 (7)	4822 (7)	6185 (11)	68 (5)
C′(4)	5632 (8)	5572 (9)	6307 (12)	81 (7)
O(4)	5010 (5)	5565 (7)	6046 (11)	115 (5)
$C^{\beta}(4)$	5604 (7)	4204 (8)	6653 (14)	98 (7)
N(5)	6021 (5)	6137 (6)	6572 (9)	62 (4)
$C^{\alpha}(5)$	5690 (7)	6823 (8)	6605 (12)	70 (6)
C′(5)	6029 (7)	7331 (8)	5837 (11)	69 (5)
O(5)	6679 (4)	7492 (6)	5913 (9)	96 (5)
$C^{\beta}(5)$	5720 (8)	7161 (10)	7713 (12)	92 (7)
$C^{\gamma}(5)$	5330 (8)	6831 (11)	8565 (16)	107 (8)
$C^{\delta}(51)$	5518 (10)	7169 (12)	9684 (15)	144 (12)
$C^{\delta}(52)$	4517 (8)	6873 (11)	8358 (16)	132 (10)
N(6)	5599 (5)	7674 (5)	5130 (9)	51 (4)
$C^{\alpha}(6)$	5858 (7)	8248 (7)	4488 (12)	60 (5)
C′(6)	5422 (7)	8941 (8)	4731 (13)	72 (6)
O(6)	4772 (4)	8894 (5)	4852 (10)	103 (5)
$C^{\beta}(6)$	5819 (7)	8088 (8)	3364 (14)	77 (7)
S(6)	6365 (2)	7333 (2)	2898 (4)	87 (2)
N(7)	5792 (6)	9538 (6)	4768 (11)	82 (5)
C(7)	5453 (7)	10202 (8)	4926 (14)	102 (7)
W(1)	8521 (6)	5669 (8)	4040 (9)	86 (5)
O(s)[b]	4946 (6)	9543 (6)	2483 (11)	109 (5)
S(s)	4954 (3)	9812 (3)	1392 (4)	66 (1)[c]
C(1)(s)	5752 (11)	9492 (11)	787 (15)	115 (6)[c]
C(2)(s)	5101 (13)	10783 (13)	1378 (19)	145 (8)[c]
S(s)′	5412 (23)	10208 (26)	1824 (37)	269 (19)[c]

[a] $U_{eq} = {}^1/_3\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i\mathbf{a}_j$. [b] The atoms in the disordered DMSO solvent molecule are designated with an s suffix. [c] Isotropic.

antiparallel β-strand where the $C^{\alpha}(1)\cdots C^{\alpha}(6)$ distance is 4.036 Å. The S–S distance of 2.027 (6) Å and the CSS angles of 106.3 (5) and 105.3 (4)° compare well with bond values of 2.028–2.037 Å and bond angle values of 102.9–107.9° determined for small cyclic peptides[13] and linear disulfides.[14]

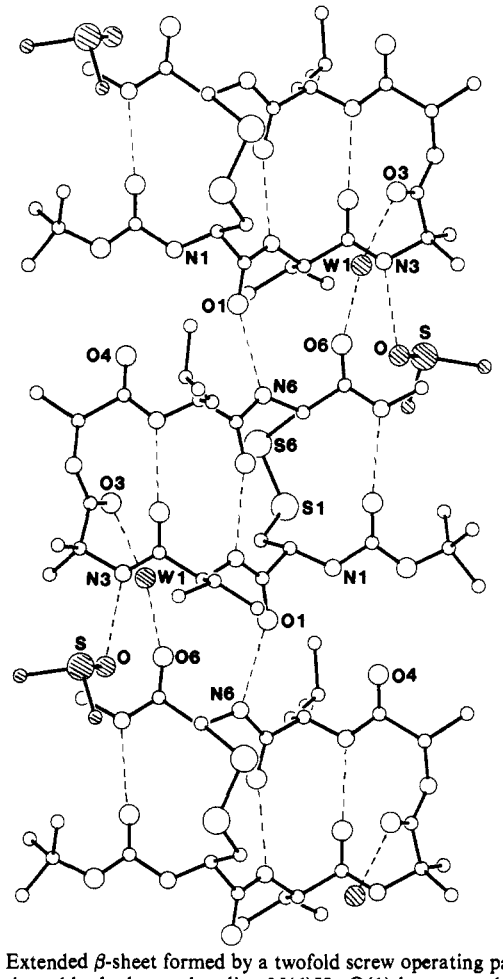

Figure 3. Extended β-sheet formed by a twofold screw operating parallel to the *a* axis and by hydrogen bonding N(6)H···O(1) between adjacent molecules. Intermolecular distances N(3)H···O(6) and N(1)H···O(4) are 0.3–0.4 Å longer than the range of values usually observed for hydrogen bonds. The solvent molecules DMSO and water (W1) are shown shaded.

The β-sheet conformation that already is present in the individual molecules is extended throughout the crystal by intermolecular hydrogen bonding. Figure 3 depicts three neighboring peptides along the *a* axis and the N(6)···O(1) hydrogen bonds that link these molecules into an infinite ribbon. A more perfect extended β-sheet would have been formed if there also were hydrogen bonds between N(1)···O(4) and N(3)···O(6). The intermolecular separations between these pairs of atoms are 3.45 and 3.32 Å, respectively, 0.3–0.4 Å longer than usual hydrogen bond lengths.

Actually, N(1) and O(4) do not participate in any hydrogen bonding. The solvent molecules DMSO and H_2O are between N(3) and O(6) in adjacent peptide molecules. A strong hydrogen bond is formed between N(3) and the O atom of DMSO. The water molecule is a donor to O(6) and O(3) in adjacent molecules in the β-sheet ribbon and an acceptor from N(4) in a neighboring ribbon related by a twofold screw. Hydrogen bond lengths are listed in Table IV.

Disulfide Conformation. In a disulfide bridge between two C^{α} atoms, $C^{\alpha}(i)$–$C^{\beta}(i)$–S(*i*)–S(*j*)–$C^{\beta}(j)$–$C^{\alpha}(j)$, there are five bonds and five torsional angles X^1, X^2, X^3, $X^{2'}$, and $X^{1'}$, respectively. In proteins, the most predominantly observed values[3] are near −60, −85, −90, −85, and −60° (the conformation called the left-hand spiral), with $C^{\alpha}(i)\cdots C^{\alpha}(j)$ separations of ~6.1 Å. For the present

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Table II. Bond Lengths (Å) and Angles (deg)[a]

	Boc, 0	Cys, 1	Val, 2	Aib, 3	Ala, 4	Leu, 5	Cys, 6	NHMe, 7
				i				
				Bonds				
N_i–C_i^α		1.438	1.423	1.489	1.494	1.420	1.427	1.403
C_i^α–C_i'		1.525	1.523	1.548	1.605	1.496	1.556	
C_i'–O_i	1.230	1.249	1.253	1.201	1.207	1.253	1.226	
C_i'–N_{i+1}	1.367	1.298	1.337	1.351	1.320	1.361	1.310	
C_i^α–C_i^β		1.524	1.525	1.486	1.535	1.537	1.455	
				1.518				
C_i^β–C_i^γ			1.520			1.439		
			1.452					
C_i^γ–C_i^δ						1.588		
						1.542		
C_i^β–S_i[b]		1.805					1.833	
				Angles				
$C_{i-1}'N_iC_i^\alpha$		122.4	126.1	119.6	120.7	119.0	121.6	120.9
$N_iC_i^\alpha C_i'$		112.4	105.9	106.4	112.5	111.4	109.3	
$C_i^\alpha C_i'N_{i+1}$	111.1[c]	116.7	118.3	116.2	116.8	118.2	115.7	
$C_i^\alpha C_i'O_i$	127.0[d]	118.0	116.7	121.2	115.4	120.7	119.0	
$N_{i+1}C_i'O_i$	121.8	125.3	124.8	122.5	127.4	120.7	125.4	
$C_i'C_i^\alpha C_i^\beta$		106.5	109.4	116.5	110.8	108.6	109.6	
				105.2				
$N_iC_i^\alpha C_i^\beta$		110.8	113.9	109.1	107.3	112.3	112.8	
				108.5				
$C_i^\alpha C_i^\beta C_i^\gamma$			111.6			119.4		
			115.2					
$C_i^\beta C_i^\gamma C_i^\delta$						112.7		
						110.4		
$C_i^\alpha C_i^\beta S_i$[b]		117.2					116.3	

[a] Esd's for bond lengths ~0.02 Å; esd's for bond angles 1.0–1.5°. [b] Bond length for S(1)–S(6) = 2.027 (6) Å; bond angles $C^\beta(1)S(1)S(6)$ = 106.3 (5)°, $C^\beta(6)S(6)S(1)$ = 105.3 (4)°. [c] ObC(0)N(1). [d] ObC(0)O(0).

Table III. Torsional Angles (deg)[a]

angle	Cys[1]	Val[2]	Aib[3]	Ala[4]	Leu[5]	Cys[6]
$\phi(N_i$–$C_i^\alpha)$	−138[b]	−130	50	−89	−119	−119
$\psi(C_i^\alpha$–$C_i')$	149	119	−131	19	126	140[c]
$\omega(C_i'$–$N_{i+1})$	170	177	−173	175	170	177[d]
χ^1	−55	−63			−66	−63
		171				
χ^2	−101				171	−84
S(1)–S(6)	101					

[a] Esd's ~1.2°. The torsion angles for rotation about bonds of the peptide backbone (ϕ, ψ, ω) and about bonds of the side chains (χ^1, χ^2) are described in ref 12. [b] With C(0) of the Boc group. [c] With N(7) of the $NHCH_3$ group. [d] With N(7)–C(7) of the $NHCH_3$ group.

Table IV. Hydrogen Bonds[a]

type	donor	acceptor	length, Å	angle (C=O···N), deg
intramolecular	N(2)	O(5)	2.854	162
	N(5)	O(2)	2.890	142
	N(7)	O(0)	2.874	175
peptide–peptide	N(6)	O(1) ($-^1/_2 + x$, $1.5 - y$, $1 - z$)	2.899	154
peptide–solvent	N(3)	O(DMSO)	2.961	
	N(4)	W(1) ($1.5 - x$, $1 - y$, $^1/_2 + z$)	3.098	
	W(1)	O(3) (x, y, z)	2.846	
	W(1)	O(6) ($^1/_2 + x$, $1.5 - y$, $1 - z$)	2.843	

[a] A more perfect extended β-sheet would also have peptide–peptide hydrogen bond between N(1)···O(4) and N(3)···O(6). These distances are 3.46 and 3.32 Å in this crystal.

structure, the five torsional angles are −55, −101, +101, −84, and −63°, with $C^\alpha(1)\cdots C^\alpha(6)$ = 4.036 Å. Although the absolute values of the torsional angles are not very different from those found in proteins, the sign sequence − − + − − is rarely found in proteins.[3] This conformation for the disulfide bridge has been called the short right-hand hook. It has not occurred between antiparallel β-strands in proteins.

The torsion about the S–S bond can occur either in the plus or minus direction with a range of values of 80–100°. The results of crystal structure analyses for small peptides with closed backbone loops containing S–S bonds are listed in Table V. The resolutions for these structure analyses are better than 0.9 Å, and the *R* factors are less than 10%, except for the last two entries.

Type II′ β-Bend for Aib. Chain reversal at Aib[3]-Ala[4] is accompanied by the formation of a type II′ β-bend with conformational angles ϕ_3, ψ_3 = 50, −131° and ϕ_4, ψ_4 = −89, 19° (see Figure 1 and Table III). Up to the present, crystallographic studies of a large number of Aib residues have failed to yield a single example of such a conformation for an Aib residue located centrally in an oligopeptide.[6-8] Aib residues tend to be helix formers (3_{10}- and α-helices) with ϕ and ψ values near ±60 and ±30°, respectively.

It is interesting to note that the type II′ β-bend in the present compound has very similar spatial characteristics to a number of aberrant β-bends for L,L residues that are type II or II′ where a type I was expected (see compounds **2**–**6** in Table VI). In each of these peptides, one L residue has "forbidden" ϕ, ψ values that fall in the D region of the Ramachandran ϕ, ψ plot.[22] One of the consequences is the very close approach of 2.81–2.87 Å between $N_{i+1}\cdots C_{i+1}^\beta$. To achieve a separation even as large as 2.81–2.87 Å, there is a distortion of the tetrahedral angles at C_{i+1}^α that opens the $C'C^\alpha C^\beta$ angle to a value of ~116°.

From these examples, it is apparent that L,L sequences, and in the present case an Aib,L sequence, can form type II or II′ β-bends and that some adjustments need to be made to the allowed regions in the classic ϕ, ψ maps.[23]

Comparison of X-ray Diffraction and Spectroscopic Results. An NMR study[1f] of the cyclic cystine peptide **1** in $CDCl_3$, established an antiparallel β-sheet conformation nucleated by a β-bend at the Aib-Ala sequence, stabilized by three intramolecular hydrogen bonds of the type Boc CO···methylamide NH, Leu CO···Val NH, and Val CO···Leu NH. These features are clearly

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Table V. Torsional Angles for S–S Bonds in Peptides

cyclic cystine peptides	loop size	X_{ss}, deg	ref
cyclo(Cys-Cys)	8-membered	−94	15
H_3N^+-Cys-Cys-COO^-	8-membered	+94	16
Boc-Cys-Cys-OCH_3	8-membered	+95.7	17
Boc-Cys-Pro-Aib-Cys-$NHCH_3$	14-membered	+82	13
Boc-Cys-Pro-Leu-Cys-$NHCH_3$	14-membered	+82	18
Boc-Cys-Val-Aib-Ala-Leu-Cys-$NHCH_3$	20-membered	+101	this paper
Cys-Tyr-Ile-Gln-Asn-Cys	20-membered	+76, −101 (2 molecules space gp *C*2) +77, −87 −94, +83 (space gp $P2_1$, disorder)	3
-Cys-Tyr-Phe-Gln-Asn-Cys-	20-membered	+95	4

Table VI. Aberrant Type II or II′ β-Bends

no.	compound	dipeptide linkage in β-bend	φ, ψ, deg: *i* + 1	φ, ψ, deg: *i* + 2	$N_{i+2}\cdots C^{\beta}_{i+1}$, Å	$O_{i+2}\cdots C^{\beta}_{i+2}$	ref
		Type II′					
1	Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe	Aib-L-Ala	50, −131	−89, 19	2.81		this paper
2	*cyclo*-(Pro-Val-Phe-Phe-Ala-Gly) I[a]	L-Phe-L-Ala	54, −118	−88, −4	2.87		19
3	*cyclo*-(Pro-Val-Phe-Phe-Ala-Gly) II[a]	L-Phe-L-Ala	60, −120	−86, −5	2.84		20
4	Cys-Tyr-Phe-Gln-Asn-Cys	L-Phe-L-Gln	55, −115	−66, −20	*b*		4
		Type II					
5	Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2	L-Ile-L-Gln	−65, 125	56, 29		*b*	3
6	*i*-Bu-Pro-Ala-*i*-PrNH_2	L-Pro-L-Ala	−59, 136	66, 14		2.84	21

[a] The crystals in **2** and **3** are polymorphs with different space groups. [b] Coordinates have not been published in preliminary papers; hence, the $N_{i+2}\cdots C^{\beta}_{i+1}$ or $O_{i+2}\cdots C^{\beta}_{i+2}$ intramolecular distances cannot be calculated.

maintained in the solid state. The NMR results suggested that peptide association occurs in an apolar solvent like $CDCl_3$ with Cys[6] NH being involved in intermolecular hydrogen bonding.[1f] Interestingly, this group is indeed involved in an intermolecular hydrogen bond in the solid state also. The major point of difference between the solution and solid-state studies is in the definition of the conformation of the Aib-Ala reverse turn. While a type I′ β-turn has been inferred from NOE studies in $CDCl_3$ ($\phi_{Aib} \sim 60°$, $\psi_{Aib} \sim 30°$, $\phi_{Ala} \sim 90°$, $\psi_{Ala} \sim 0°$), a type II′ β-turn is observed in the crystalline state ($\phi_{Aib} = 50°$, $\psi_{Aib} = -131°$, $\phi_{Ala} = -89°$, $\psi_{Ala} = 19°$). Since the crystals were obtained from $(CD_3)_2SO$ solution, a comparison of the relevant NOEs in the two solvents was effected, and the results are presented in Table VII. The NOEs Aib CH_3 (high-field resonance) ↔ Aib NH and Aib CH_3 (low-field resonance) ↔ Aib NH have similar magnitudes in both solvents suggesting that ϕ_{Aib} distributions are similar. The NOE Ala CH_3 ↔ Ala $C^{\alpha}H$, which is independent of backbone conformation, also shows little change on going from $CDCl_3$ to $(CD_3)_2SO$. In fact, there is little change in NOEs except for two key interactions as solvent is changed from $CDCl_3$ to $(CD_3)_2SO$. The two that change are the Aib $C^{\beta}H_3$ ↔ Ala NH (low-field resonance) and the Ala NH ↔ Ala $C^{\alpha}H$. The presence of competing dipolar relaxation pathways with other proximate protons (cf. Aib $C^{\beta}H_3$) precludes quantitative analysis of the various NOEs to Ala NH. Nevertheless, the large changes for the two interactions stated above are consistent with a shift from a predominantly type I′ β-turn to a greater proportion of type II′ β-turn. The relevant interproton distances observed in the crystals are indicated in Figure 4.

Table VII. NOEs Observed between Protons in the Aib-Ala Segment

resonance: irrad	resonance: obsd	NOE, %: $CDCl_3$[a]	NOE, %: $(CD_3)_2SO$[b]
Aib $C^{\beta}H_3$ (high field)	Aib NH	6.6	6.4
	Ala NH		1.2
Aib $C^{\beta}H_3$ (low field)	Aib NH	1.8	1.8
	Ala NH	11.0	4.0
Ala $C^{\beta}H_3$	Ala NH		2.0
	Ala $C^{\alpha}H$	11.8	9.2
Ala NH	Aib $C^{\beta}H_3$ (low field)	3.4	1.2
	Aib $C^{\beta}H_3$ (high field)	0.3	0.3
	Ala $C^{\beta}H_3$		1.0
	Ala $C^{\alpha}H$	5.3	14.0

[a] 293 K. [b] 343 K.

Circular dichroism studies in a wide range of organic solvents yielded a strong negative CD band for the long-wavelength S–S $n \rightarrow \sigma^*$ transition. The observed CD parameters λ, nm ($[\theta]_M$,

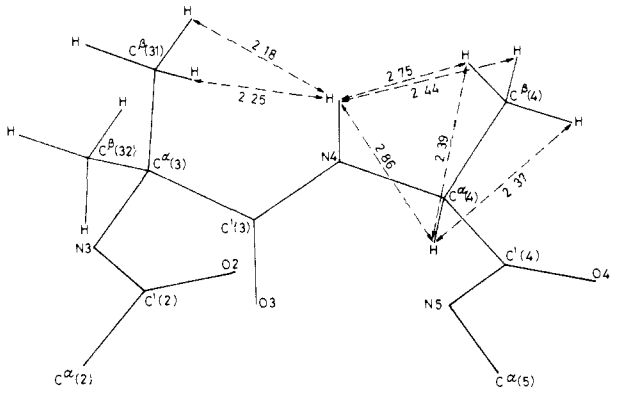

Figure 4. Schematic representation of the Aib-Ala type II′ β-turn segment with interproton distances as found in the crystal. Double-edged arrows indicate diagnostically useful NOEs. In solution the methyl groups may be rotating.

deg cm^2 dmol^{-1}) are as follows: $CHCl_3$, 270 (−6550); $(CH_3)_2CO$, 273 (−2750); dioxane, 268 (−6250); dioxane–hexane (1:1), 260 (−7750); methanol, 270 (−4000); methanol–water (1:1), 270 (−3000); trifluoroethanol, 272 (−2530); trimethyl phosphate, 272 (−2950). The relatively high ellipticity values in apolar solvents are characteristic of a conformationally rigid disulfide chromophore.[24] The observed negative sign of the CD band is consistent with a right-handed chirality having $\chi_{SS} \sim 110 \pm 10°$, as suggested for a 2,7-cystine-gramicidin S analogue.[25] This is an excellent agreement with the χ_{SS} value of 101° in the crystal structure. In more polar solvents, the diminished ellipticity values suggest enhanced flexibility about the S–S linkage.

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Registry No. 1, 112159-35-0.

Supplementary Material Available: Tables of anisotropic thermal parameters of non-hydrogen atoms and atomic coordinates of hydrogen atoms (2 pages); observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.

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Communications to the Editor

Stereoselective Total Synthesis of (±)-Atisine via Intramolecular Double Michael Reaction

Masataka Ihara,† Makoto Suzuki,† Keiichiro Fukumoto,*† Tetsuji Kametani,‡ and Chizuko Kabuto§

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Institute of Medicinal Chemistry, Hoshi University Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan
Instrumental Analysis Center for Chemistry Faculty of Science, Tohoku University Aobayama, Sendai 980, Japan

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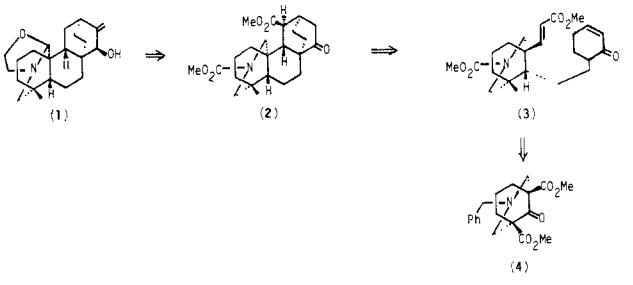
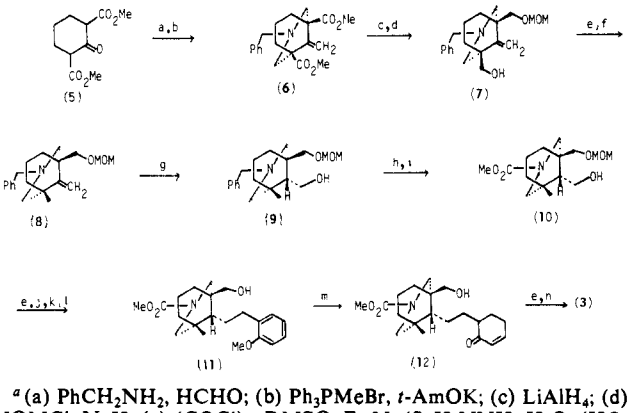
Atisine, the predominant alkaloid of *Aconitum heterophyllum*, possesses a unique hexacyclic structure **1** including azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane rings[1] and has attracted the attention of synthetic organic chemists as a target molecule due to its architectural features. Three different routes[2] have been successful in reaching Pelletier's synthetic intermediates[3,4] for atisine. Recently a new methodology for construction of bicyclo[2.2.2]octane skeleton employing an intramolecular double Michael reaction was developed by us.[5] We envisioned assembly of a synthetic intermediate **2** of the aconitium alkaloid by its exploitation and preparation of the substrate **3** of the key reaction starting from a symmetrical azabicyclo[3.3.1]nonane derivative **4**. Here we wish to communicate a stereocontrolled formal total

Scheme I



Scheme II[a]



[a] (a) $PhCH_2NH_2$, HCHO; (b) Ph_3PMeBr, *t*-AmOK; (c) $LiAlH_4$; (d) MOMCl, NaH; (e) $(COCl)_2$, DMSO; Et_3N; (f) $H_2NNH_2 \cdot H_2O$, $(HOCH_2CH_2OCH_2)_2$, NaOH, 150 → 180 °C; (g) $NaBH_4$, $BF_3 \cdot Et_2O$, $(MeOCH_2CH_2)_2O$; $Me_3N \rightarrow O$; (h) 10% Pd-C, HCO_2NH_4; (i) $ClCO_2Me$, K_2CO_3; (j) *o*-methoxybenzyltriphenylphosphonium bromide, *n*-BuLi; (k) H_2, 10% Pd-C; (l) concentrated HCl; (m) Na, liquid NH_3, EtOH, diluted HCl; (n) $Ph_3P{=}CHCO_2Me$.

† Pharmaceutical Institute, Tohoku University.
‡ Hoshi University.
§ Instrumental Analysis Center for Chemistry, Tohoku University.

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