The Crystal and Molecular Structure of N-Methyl-N-t-butyl-3-hydroxyazetidinium Methanesulfonate, a Nonplanar Azetidinium Ring[1]

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Abstract: The crystal structure of N-methyl-N-t-butyl-3-hydroxyazetidinium methanesulfonate (HAM) has been determined by Patterson and Fourier methods. The space group is Pnam, No. 62, having four molecules in the orthorhombic unit cell with $a = 21.714$, $b = 7.608$, and $c = 7.360$ Å. Each molecule is bisected by a mirror plane. The sulfur atom was located in the E^2-1 Patterson synthesis, but the contribution of this atom was insufficient to determine the phases for an approximate structure. Superposition methods were used to locate the remaining atoms. The azetidinium ring is found to be buckled by $14 \pm 1°$ from a plane which'is perpendicular to the molecular mirror plane. The hydroxy and N-methyl ring substituents lie on the convex side of the ring, while the t-butyl group lies on the concave side. Only one hydrogen-bonding situation is found, and that may be interpreted as a bifurcated hydrogen bond from the hydroxyl hydrogen atom to two of the methanesulfonate oxygen atoms. The ring bond lengths in HAM are close to those of L-azetidine-2-carboxylic acid, and the degree of ring buckling is similar.

K nowledge of the detailed structure of the azetidine ring is of great importance in interpreting the results of chemical and biological transformations involving this ring system. However, despite the increasing interest in the chemistry and biochemistry of this heterocyclic system, there were no crystallographic studies of simple nonfused-ring azetidine or azetidinium compounds.[4,5] We have therefore undertaken an extensive study[6] of some of the more interesting compounds having azetidine or azetidinium rings with a view toward determining the detailed structure of this heterocyclic ring system.

Indeed, the entire problem of the geometry of the four-membered ring compounds remains a fascinating one. Cyclobutane itself is known from a variety of spectroscopic measurements to be nonplanar[7] with a dihedral angle θ of from 100 to 145°. The structure of substituted cyclobutane compounds presents a relatively complicated picture since many planar and nonplanar examples are known. Octafluorocyclobutane,[8] octa-

chlorocyclobutane,[9] and the photodimer 1,2,3,4-tetrabromo-1,2:3,4-diphthaloylcyclobutane[10] are puckered, but octahydroxycyclobutane,[11] tetraphenylcyclobutane,[12] and the photodimer of cyclopentenone[13] are planar.

While both cis- and trans-1,2-dibromo-1,2-dicarbomethoxycyclobutane[14] and cis-1,3-cyclobutanedicarboxylic acid[15] are known to be nonplanar, the corresponding trans-diacid is planar.[16] Although cyclobutanone itself is planar[17] it appears that the majority of substituted cyclobutanones are nonplanar.[18] Additional examples of nonplanar cyclobutane compounds can be cited.[15,19-22]

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(3) Recipient of Public Health Service Research Career Development Award No. K4 GM 17,620-01 from the National Institute of General Medical Sciences.

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The situation is expected to be equally complicated for the four-membered heterocyclic ring systems, the oxetanes, thietanes, and azetidines. In the case of the oxygen heterocycles it has been determined that oxetane is effectively planar.[23,24] If it is accepted that the unbonded electron pairs on oxygen present significantly less steric bulk than a carbon-bonded hydrogen, then it is evident that the effect of substituting the oxetane oxygen atom for the corresponding methylene group of a cyclobutane is to reduce substantially vicinal and cross-ring steric interactions. The results for oxetane stand in apparent contrast to those for thietane, which is apparently puckered,[25] although this result is subject to some disagreement.[26]

The only published structures involving derivatives of the azetidine ring were fused-ring 2-azetidinone derivatives found in antibiotics. Not surprisingly ring systems such as the 2-azetidinone or 2-azetidinethione having sp²-hybridized carbons are effectively planar.[27] However, the azetidine ring can be treated as if it is a structure composed of sp³-hybridized atoms.[28] This is consistent with the basicity[29] of azetidine derivatives, as well as their ability to function as electron donors in the formation of complexes with trimethylboron.[30] The basicity and hybridization of the four-membered ring compounds very much resemble the corresponding properties of the five-membered pyrrolidine ring system but contrast sharply with the three-membered ring aziridines which are much less basic.

From the preceding results it should be apparent that the precise geometry of the azetidine or azetidinium ring could not be readily predicted by analogy with other four-membered ring compounds and for this reason we undertook a study of azetidine and azetidinium compounds.

Experimental Section

The synthesis of 1-t-butyl-3-hydroxyazetidine was carried out after the methods of Gaertner.[31] Epichlorohydrin and t-butylamine were allowed to react together in methanol at room temperature for 3 days and at 60° for 6 days. The solvent was evaporated and the remaining solid was triturated with warm acetone. Recrystallization of the remaining solid from a mixture of isopropyl and ethyl alcohols gave 1-t-butyl-3-hydroxyazetidine hydrochloride, mp 161–163°. Treatment of the hydrochloride with aqueous sodium hydroxide followed by extraction with ether gave the free amine which crystallized on evaporation of the ether (mp 40–41°; lit.[31] mp 45–46°). The 1-t-butyl-3-hydroxyazetidine was treated with an equimolar amount of methyl methanesulfonate dissolved in 40% hexane–60% methanol for 12 hr. Evaporation of the solvent gave a white solid which was washed three times with ether. Samples were recrystallized from isopropyl alcohol. Crystalline 1-methyl-1-t-butyl-3-hydroxyazetidinium methanesulfonate (HAM) was obtained with mp 188–191°.

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Anal. Calcd for $C_9H_{21}NO_4S$: C, 45.16; H, 8.84; N, 5.85; S, 13.40. Found: C, 45.28; H, 8.62; N, 5.79; S, 13.20.

The prismatic crystals displayed well-formed [111] and [100] faces. One such crystal was selected having approximate dimensions of 0.2 mm in each direction, and was mounted on the tip of a 50-μ glass fiber using Ambroid cement thinned with nitrobenzene. Precession photographs were taken and diffractometer intensity data were collected for 2145 independent reflections using Mo Kα radiation. For the low-angle region up to $\lambda d^* = 0.50$, constant-velocity 2θ scans and balanced filters were used. For the remainder of the data, up to $\lambda d^* = 1.25$, unequal-interval nine-point step scans and β filtration were used. Owing to the short counting times employed, the small crystal size, and the high-angle regions of reciprocal space being covered, 966 of the measured reflections were observed, while the remaining 1179 were indistinguishable from background and were unobserved. Absorption corrections were not applied, due to the nearly equidimensional shape, low absorption coefficient, and small size of the crystal. Table I lists the crystal data.

Table I. Crystal Data for N-Methyl-N-t-butyl-3-hydroxyazetidinium Methanesulfonate
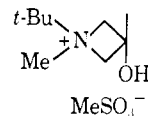
$C_9H_{21}NO_4S$
Mol wt 239.33
Orthorhombic, space group Pnam
   (based on refinement)
$Z = 4$
Molecular symmetry M
$a = 21.714 \pm 0.009$ Å
$b = 7.608 \pm 0.006$ Å
$c = 7.360 \pm 0.007$ Å
$D_m = 1.34 \pm 0.01$ g cm^{-3}
$D_x = 1.308$ g cm^{-3}
$\mu_{MoK\alpha} = 2.78$ cm^{-1}

Structure Determination and Refinement

An initial E²-1 Patterson synthesis was calculated in which an outstanding peak was located in the Harker section and at corresponding coordinates along the Harker lines. This peak was assumed to represent a sulfur–sulfur interaction, and the sulfur location was used in the application of superposition methods,[32] making further use of the E²-1 synthesis. Two- and four-atom multiple minimum functions were calculated with the symmetry of the space group added, producing a number of strong peaks near $Z = 0$ in the resulting maps. After using these peaks in additional multiple minimum function calculations, the most frequently recurring 15 peaks were assumed to be atomic locations, and structure factor and Fourier calculations were made assuming the noncentrosymmetric space group Pna2₁. At this stage, no recognizable molecular features could be seen. The resulting electron density contained 13 of the 15 atoms which were assumed beforehand, plus two additional peaks in likely places for a reasonable trial model of the structure.

The trial model so obtained was refined isotropically, using only 600 reflections of lower sin θ/λ, to an agreement index of 0.12 with Shiono's version[33] of the Busing, Martin, and Levy least-squares program.[34] At this

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Table II. Atomic Positional and Thermal Parameters in HAM. Final Pnam Refinement

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S	0.3858 (1)	0.6049 (2)	0.2500	0.0018 (1)	0.0142 (3)	0.0197 (4)	0.0006 (1)		
O(1)	0.2794 (3)	0.2346 (8)	0.2500	0.0028 (2)	0.0207 (13)	0.0386 (19)	0.0025 (4)		
O(2)	0.3977 (3)	0.7910 (7)	0.2500	0.0049 (3)	0.0137 (11)	0.0259 (15)	0.0009 (4)		
N	0.1722 (3)	0.5472 (7)	0.2500	0.0016 (2)	0.0124 (10)	0.0106 (10)	0.0000 (3)		
C(1)	0.1922 (3)	0.7262 (9)	0.2500	0.0015 (2)	0.0121 (13)	0.0233 (18)	−0.0017 (4)		
C(3)	0.2182 (3)	0.2954 (9)	0.2500	0.0020 (2)	0.0139 (14)	0.0193 (17)	0.0006 (4)		
C(5)	0.1004 (3)	0.5532 (9)	0.2500	0.0013 (2)	0.0152 (13)	0.0152 (14)	−0.0004 (4)		
C(7)	0.0760 (4)	0.3604 (10)	0.2500	0.0020 (2)	0.0162 (15)	0.0247 (20)	−0.0018 (4)		
C(9)	0.4569 (4)	0.5015 (11)	0.2500	0.0017 (2)	0.0251 (19)	0.0252 (20)	0.0003 (5)		
O(3)[a]	0.3551 (2)	0.5469 (6)	0.4123 (7)	0.0035 (1)	0.0262 (10)	0.0502 (16)	0.0014 (3)	0.0090 (4)	0.0109 (11)
C(2)	0.2004 (2)	0.4295 (6)	0.3955 (7)	0.0019 (1)	0.0143 (9)	0.0179 (11)	0.0006 (3)	−0.0009 (3)	0.0013 (9)
C(6)	0.0788 (2)	0.6455 (7)	0.4225 (8)	0.0017 (1)	0.0226 (12)	0.0263 (14)	0.0001 (3)	0.0009 (4)	−0.0052 (13)

Coordinates not refined

				$B_{\text{isotropic}}$
H(C11)	0.247	0.70	0.250	2.0
H(C12)	0.188	0.788	0.370	2.0
H(C21)	0.170	0.410	0.500	2.4
H(C22)	0.240	0.499	0.450	2.4
H(C3)	0.195	0.170	0.250	1.8
H(C61)	0.101	0.776	0.435	2.1
H(C62)	0.097	0.552	0.530	2.1
H(C63)	0.034	0.645	0.418	2.1
H(C71)	0.030	0.374	0.250	2.1
H(C73)	0.090	0.290	0.370	2.1
H(C92)	0.483	0.540	0.350	2.8
H(C93)	0.447	0.360	0.250	2.8
H(O1)	0.315	0.340	0.250	3.7

[a] Atoms O(4), C(4), and C(8) (not listed) are related by the mirror plane at $z = {}^1/_4$ to atoms O(3), C(2), and C(6), respectively.

Table III. Principal Axes of Thermal Ellipsoids[a]

Atom	i	U_i, Å	$U_i \cos \theta_{ia}$, Å	$U_i \cos \theta_{ib}$, Å	$U_i \cos \theta_{ic}$, Å
S	1	0.193 (1)	0.119	−0.152	0
	2	0.221 (1)	−0.174	−0.137	0
	3	0.233	0	0	0.233
O(1)	1	0.205 (2)	0.134	−0.155	0
	2	0.292 (4)	−0.221	−0.191	0
	3	0.326	0	0	0.326
O(2)	1	0.198 (2)	−0.019	0.197	0
	2	0.267 (4)	0	0	−0.267
	3	0.342	0.340	0.033	0
N	1	0.170 (2)	0	0	0.170
	2	0.190 (4)	0.027	−0.188	0
	3	0.197	0.195	0.028	0
C(1)	1	0.146 (2)	0.104	0.103	0
	2	0.222 (5)	−0.156	0.158	0
	3	0.253	0	0	0.253
C(3)	1	0.195 (2)	0.093	−0.171	0
	2	0.225 (5)	−0.198	−0.107	0
	3	0.230	0	0	0.230
C(5)	1	0.172 (2)	0.167	0.041	0
	2	0.204 (5)	0	0	−0.204
	3	0.213	−0.051	0.207	0
C(7)	1	0.181 (2)	0.128	0.128	0
	2	0.249 (5)	−0.176	0.176	0
	3	0.260	0	0	0.260
C(9)	1	0.200	0.200	−0.013	0
	2	0.263 (5)	0	0	−0.263
	3	0.272	0.017	0.262	0
O(3)	1	0.178 (1)	0.138	0.037	−0.106
	2	0.264 (3)	0.084	−0.249	0.023
	3	0.444 (5)	0.241	0.114	0.353
C(2)	1	0.185 (1)	0.116	−0.114	0.087
	2	0.216 (3)	−0.106	−0.170	−0.080
	3	0.234 (5)	0.141	0	−0.187
C(6)	1	0.197 (1)	0.185	−0.035	−0.055
	2	0.237 (4)	−0.074	−0.182	−0.132
	3	0.291 (5)	0.032	−0.178	0.228

[a] The root mean square displacement U_i corresponds to the ith principal axis of the ellipsoid and $U_i \cos \theta_{ia}$, $U_i \cos \theta_{ib}$, and $U_i \cos \theta_{ic}$ are the root mean square components of thermal displacement along principal axis i projected on crystallographic axes a, b, and c.

point, anisotropic temperature factors were applied to the 15 atoms and further refinement, using all 966 observed reflections and a weighting scheme suggested by Hughes,[35] brought the agreement index to a value of 0.11.

A difference Fourier synthesis after the preceding refinement cycle gave easily recognizable peaks for all of the 21 hydrogen atoms. Their positions were all chemically reasonable, falling within ±0.14 Å of the expected value of 1.08 Å from the carbons or 0.98 Å from the oxygen to which they were attached. The hydrogen atoms were then assigned isotropic temperature factors based on those of the atoms to which they are bonded, and further least-squares refinement was carried out keeping hydrogen atoms fixed. Still using space group Pna2$_1$, the agreement index was 0.090 and the weighted value was 0.061.

Inspection of the refined model followed by a negative piezoelectric test suggested a refinement in the centrosymmetric space group Pnam, keeping hydrogen atoms fixed as before. The resulting model gave lower standard deviations and more reasonable thermal parameters, although the agreement index increased to 0.100, with a weighted value of 0.061. This increase is reasonable in view of the reduction from 135 to 82 parameters refined.

The structure factors from the final refinement and coordinates from the preliminary refinement are available from the authors. The final atomic parameters for Pnam are listed in Table II and the root mean square atomic displacements in Table III.

Description of the Structure

A stereoview of the molecule produced by the Oak Ridge Plotting Program[36] is shown in Figure 1, and Ta-

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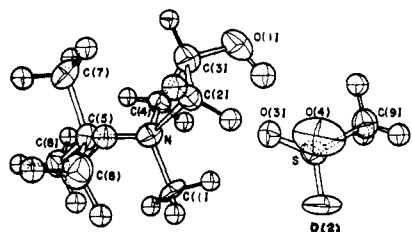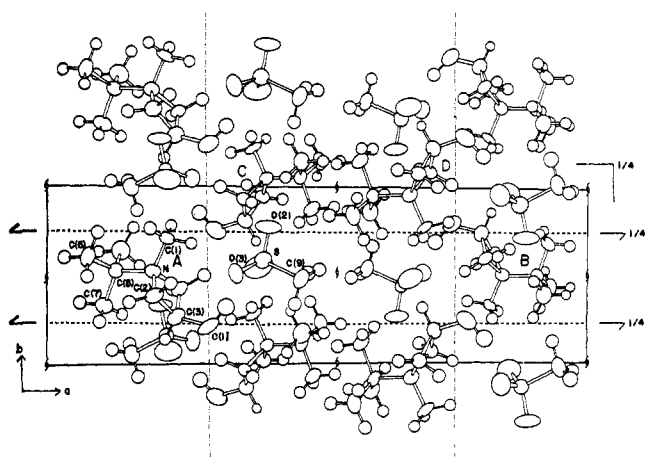
Figure 1. Stereoscopic view of the molecule.

Figure 2. Perspective drawing of the structure of N-methyl-N-t-butyl-3-hydroxyazetidinium methanesulfonate as viewed along a line parallel to the c axis. The symmetry code for the molecules is $A = x, y, z;$ $B = 1 - x, 1 - y, -\frac{1}{2} + z;$ $C = \frac{1}{2} - x, \frac{1}{2} + y, -\frac{1}{2} + z;$ $D = \frac{1}{2} + x, \frac{3}{2} - y, z.$

ble IV lists the interatomic distances and angles. The entire structure, including the methanesulfonate ion which is hydrogen bonded to an azetidinium ion, is split by the mirror plane. As in the case of L-azetidine-2-carboxylic acid,[4] the ring is buckled. The dihedral angle between the planes N–C(2)–C(4) and C(3)–C(2)–C(4) is 166 ± 1°, very close to the 169 ± 1° observed in the carboxylic acid. The substitutents at N and C(3) are located such that the less bulky methyl group is opposite the hydroxyl group across the convex side of the ring, while the t-butyl group faces only a hydrogen atom at C(3) across the concave side of the ring. The t-butyl group is so oriented that the N-methyl group lies between two opposing methyl groups attached to the tertiary carbon atom.

It was anticipated[37] that the major product of quaternization of N-t-butyl-3-hydroxyazetidine would arise from the quaternization of conformer Ia rather than Ib. This was expected because the conformational inversion between Ia and Ib should significantly favor Ia,[37] because azetidines are strongly basic amines,[29] and because methyl methanesulfonate is a quaternizing agent which possesses low steric bulk together with an excellent leaving group. Since the nuclear magnetic resonance spectrum of the crude reaction product is practically identical with that of the recrystallized material used for the present study, it is probable that conformer Ia does indeed greatly predominate over Ib in solution.

The azetidine ring lies perpendicular to the molecular mirror plane so that C(2) and C(4) are in a line parallel

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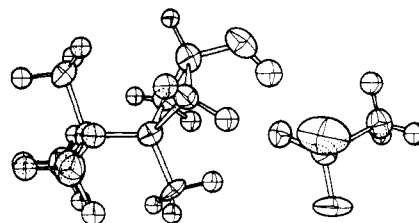
to the c axis (Figure 2). A methanesulfonate ion is associated with the hydroxyl group of each molecule through a "bifurcated" hydrogen bonding system.
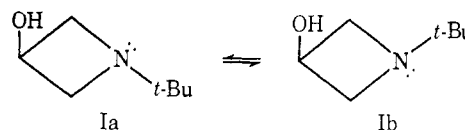
The H(O1) and the donor O(1) atoms both lie on the mirror plane, and the acceptor O(3) and O(4) atoms are required by mirror symmetry to be equidistant from the H(O1) atom on that mirror plane.

Table IV. Distances and Angles

i	j	k	D_{ij}, Å	D_{jk}, Å	Angle (ijk), deg
		(a)	Azetidinium group		
C(1)	N	C(2)	1.484 (9)	1.525 (8)	112.2 (5)
		C(5)		1.560 (9)	111.7 (5)
C(2)	N	C(4)	1.525 (8)	1.525 (8)	89.2 (4)
N	C(2)	C(3)	1.525 (8)	1.528 (8)	90.0 (4)
C(2)	C(3)	C(4)	1.528 (8)	1.528 (8)	88.9 (4)
		O(1)		1.409 (9)	117.2 (5)
C(3)	O(1)	H(O1)	1.409 (9)	1.11 (2)	114.8 (1.3)
		(b)	Methanesulfonate group		
O(2)	S	C(9)	1.439 (6)	1.734 (9)	106.6 (4)
		O(3)		1.438 (5)	112.6 (3)
O(3)	S	O(4)	1.438 (5)	1.438 (5)	112.3 (3)
		C(9)		1.734 (9)	105.9 (4)
		(c)	t-Butyl group		
C(6)	C(5)	C(7)	1.525 (8)	1.560 (10)	109.1 (5)
		C(8)		1.525 (8)	112.7 (5)
		N		1.560 (9)	108.7 (5)
C(7)	C(5)	C(8)	1.560 (10)	1.525 (8)	109.1 (5)
		N		1.560 (9)	108.2 (5)
		(d)	Hydrogen bonding		
O(1)	H(O1)	O(3)	1.11 (2)	2.16 (2)	143.6 (1.7)
C(3)	O(1)	O(3)	1.409 (9)	3.126 (9)	104.3 (5)

It is not certain that the bifurcated hydrogen bonding system has exact mirror symmetry, since if it were slightly asymmetric and disordered the diffraction effects would show only an average structure with mirror symmetry. To determine whether or not the acceptor O(3) and O(4) atoms are thus slightly disordered, we see that the major axes of their thermal ellipsoids do in fact point toward the H(O1) atom, implying that we may have only the average positions of O(3) and O(4). On the other hand, this vibration amplitude (see Table III) is less than three times the smallest amplitude for these ε ~~~~~~~~~~~~~~~~~~~~~~~~~~~~ libration of the *Journal of the American Chemical Society* possible to say whether or not the bifurcated hydrogen bonding system is exactly symmetrical.

There is no other hydrogen bonding in the structure. Instead the molecules are held together largely by van der Waal's forces between the methyl and *t*-butyl parts of the azetidinium ions, and by similar forces between the methyl groups of the methanesulfonate ions.

The S–O distances in the methanesulfonate group are 1.438 and 1.439 Å, identical within experimental error. Cesium methanesulfonate[38] has two different S–O distances, 1.434 and 1.485 Å, but Brandon and Brown[38] suggest that an average of these may be as realistic. Since their error must therefore be about ±0.03 Å, a more reliable S–O distance is probably given by the present study.

The S–C distance of 1.73 Å is on the short end of the range reported for S–C bond lengths[39] although a bond length of 1.79 Å is reported for the case of dimethyl sulfone.[40] The bond lengths and angles in the *t*-butyl group appear normal.

The azetidinium ring geometry is similar to that of azetidinecarboxylic acid:[4] the ring is not planar, the bond angles are remarkably close to 90°, and the bond lengths are almost the same. The C–N distances, 1.525 Å, are not significantly different from the C–C ring distances of 1.528 Å, although these are not so close in azetidinecarboxylic acid. The average ring distance in HAM is 1.527 Å compared with 1.523 Å in azetidine-

carboxylic acid, which leads us to conclude that the ring bond lengths are identical within experimental error.

The degree of puckering of the ring is not large compared to some cyclobutane compounds. The out-of-plane bending in this structure is 14 ± 1°, quite similar to the 11 ± 1° puckering found for the case of azetidinecarboxylic acid. While small, these values are still consistent with the assumption made by Gaertner[41] in his interpretations of steric and entropic effects on ring-opening alkylations of azetidinium cations. We would anticipate, however, that planar azetidinium derivatives will be found. Thus, the results of the present study should not be taken to suggest that azetidines or azetidinium compounds will necessarily be nonplanar, but that steric effects due to specific ring substituents bring about a nonplanar ring conformation in the present case.

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The Crystal and Molecular Structure of L-Azetidine-2-carboxylic Acid. A Naturally Occurring Homolog of Proline[1,2]

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Abstract: The crystal structure of L-azetidine-2-carboxylic acid (AzCOOH) has been determined by application of superposition methods using an E^2-1 Patterson synthesis. The data were collected on a four-angle Picker automatic diffractometer using θ–2θ scan. The space group is $P2_12_12_1$, with four molecules in a unit cell of dimensions $a = 7.457$, $b = 9.810$, and $c = 6.328$ Å. The molecule is in the zwitterionic form. Both hydrogen atoms on the nitrogen atom act as hydrogen-bonding donors to the oxygen atoms in neighboring molecules. The single hydrogen atom attached to the α carbon atom is a hydrogen-bond donor to a nearby carboxylate oxygen atom. The azetidine ring is buckled by 11° from a plane so that the carboxylate group lies farther from C(4), the distal ring carbon, than would be the case for a planar ring. The conformation of AzCOOH resembles those of proline and hydroxyproline, but its substitution for either of these amino acids in a polypeptide could bring about conformation changes sufficient to significantly alter the tertiary structure of the polypeptide.

L-Azetidine-2-carboxylic acid (AzCOOH) is a naturally occurring amino acid homologous with proline from which it differs by the loss of one methylene group

from the ring.[5] From 11 to 76% of the total amino and imino acid nitrogen present in ethanolic extracts of certain plants may be due to AzCOOH; so far this imino