X-Ray and NMR Studies on Thiazolidines: Crystal Structure and Conformational Equilibria of *N*-Acetyl-2-(*p*-tolyl)thiazolidine-4-carboxylic Acid and Related Thiazolidine Derivatives[1a]

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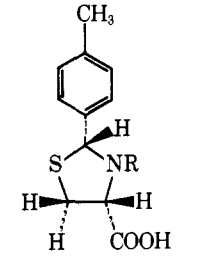
Abstract: The stereochemistry and conformational equilibria of *N*-acetyl-2-(*p*-tolyl)thiazolidine-4-carboxylic acid have been determined by x-ray crystallography and correlated with NMR spectroscopy. The tolyl was found to be cis to the carboxylic acid group, and the absolute configuration of the asymmetric centers determined by utilizing the anomalous dispersion of x rays is 2*R*,4*R*. The crystal (of unit cell constants at 22 ± 3 °C: a = 15.333 (8) Å, b = 8.320 (1) Å, c = 10.814 (1) Å, β = 96.44 (1)°) contains in its asymmetric unit two molecules of different conformation, differing mainly by torsional angle differences in the thiazolidine ring and the orientation of the tolyl groups about the C(2)–C(1′) bond. The thiazolidine ring was found to be in the "twist" conformation with the S and C(5) atoms displaced in opposite directions with respect to the plane of C(2), N(3), and C(4); the best plane through four atoms of the ring omits the sulfur. Two distinct conformations could also be detected in different polar solvents using NMR spectroscopy. At room temperature in Me_2SO-d_6, the major conformer comprises 76% of the mixture and is characterized by well-separated geminal 5-CH_2 protons and greater coupling constants of its ABX system than the minor conformer. On heating to 70 °C and above, proton resonances of the two forms are averaged out. In contrast, 2-(*p*-tolyl)thiazolidine-4-carboxylic acid showed two distinct conformers even at elevated temperatures in Me_2SO-d_6 solution. It is not possible to deduce unequivocally conformations of the two conformers based on the coupling constants of C(4) and C(5) protons, especially since the Karplus treatment is less reliable for the heterocyclic systems. However, NMR data and spin-lattice relaxation time measurements of the resolvable protons in the two conformers are consistent with general conclusions derived from x-ray crystallography as regards to the existence of the two twist conformers, although structurally different conformers could not be ruled out. ^{13}C NMR spectra of the two conformers indicate considerable shift in the relative position of C(5) resonances in the two conformers, as could be expected from the involvement of this atom in the twist conformations. Thiazolidine-4-carboxylic acid was found to exist in one conformer in the solid state; the NMR spectrum of this compound indicates only one species in the solution. When the compound is N-acetylated, two conformers can be clearly distinguished by NMR spectroscopy. The change in hybridization of N from sp^3 in thiazolidine-4-carboxylic acid to sp^2 in the present N-acetylated molecule did not result in any flattening of the ring. Short hydrogen bonds of 2.585 (4) Å and 2.605 (4) Å connect the OH of one molecule to the keto oxygen of the acetyl group of a neighboring molecule related by crystallographic symmetry.

Introduction

Reaction of carbonyl compounds with vicinal aminothiols, particularly with cysteine and related compounds, are of chemical, biochemical, and pharmacological interest and have been investigated extensively (see, for recent reviews, ref 2 and 3). On the one hand, these reactions have been pertinent to the biological activity of aminothiol compounds such as penicillamine, and on the other hand such interactions have been invoked for various natural carbonyl compounds, such as pyridoxal phosphate and carbohydrates with cysteine containing peptides and proteins,[2,3] and in model studies involving condensation of retinaldehyde.[4] It has been shown that certain carcinostatic aldehydes interact with cysteine to form thiazolidine derivatives in vivo.[5] Several thiazolidine derivatives were found to have radioprotective activity.[6]

Our interest in thiazolidine derivatives stem from their usage for blocking the SH and NH_2 groups in the synthesis of potential antagonist of L-cysteine[7,18] and as a model for the interaction of pyridoxal or its 5-phosphate with L-cysteine and penicillamine. The latter condensation is of considerable interest as an active-site probe for pyridoxal phosphate containing enzymes. For this purpose, we have condensed L-cysteine with some aldehydes such as *p*-tolualdehyde to the corresponding thiazolidine derivative I (which probably exists as a zwitterion in solution), which was then N-acetylated to II.

The configuration and conformational preferences of the thiazolidine ring system have an important bearing on the interpretation of NMR spectra of cysteine and its conformations in solutions.[8,9] While a number of 2-substituted thiazolidine derivatives have been prepared,[10] the stereochemistry of the 2 position is largely unknown. NMR was used to study the absolute stereochemistry at C(2) of thiazolidine derived from *R*-penicillamine and aldehyde.[11] The conformation of related heterocyclic ring systems has been reviewed,[12] and more recently, conformation of related thiazolidines has been studied by NMR spectroscopy[13,14] and by x-ray crystallography.[15-17] In our present study, we have determined the structure and absolute stereochemistry of II by x-ray crystallographic techniques. We have attempted to correlate the conformational details obtained from x-ray crystallography with information obtained by NMR spectroscopy.



I, R = H; II, R = $COCH_3$

Experimental Section

The synthesis of the thiazolidine derivatives has been described elsewhere.[18]

A. Crystallography. The compound II was crystallized from ethanol. The crystals are monoclinic with unit cell constants at (22 ± 3) °C: a = 15.333 (8) Å, b = 8.320 (1) Å, c = 10.814 (1) Å, β = 96.44 (1)°.

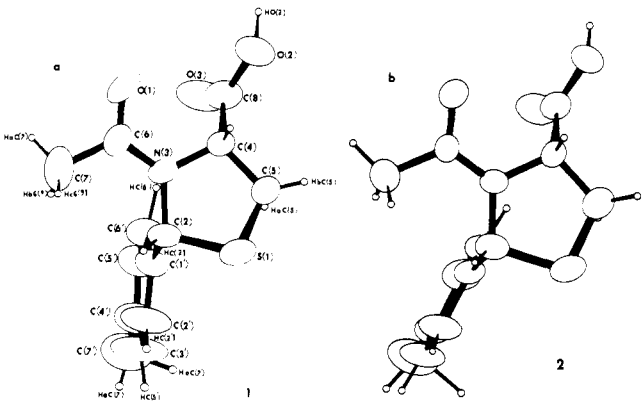


Figure 1. The absolute stereochemistry of II (a) molecule 1; (b) molecule 2. The thiazolidine rings in the two molecules are slightly different conformationally. The tolyl groups have different rotation angles about C(2)–C(1′). The view is normal to the plane through N(3), C(2), and C(4).

The $0k0$ reflections with k odd are systematically absent. The observed density of 1.34 g cm^{-3} indicates that there are four molecules in the unit cell. Consequently, two space groups have to be considered: $P2_1$ with two molecules in the asymmetric unit or $P2_1/m$ with one molecule in the asymmetric unit. We initially chose $P2_1$ and carried out the structure analysis. The subsequent structural solution and its successful refinement and the observable anomalous dispersion effects[19] clearly confirmed our choice of $P2_1$. The unit cell constants were refined (and their standard deviations estimated) by a least-squares refinement of the 2θ values of 35 reflections at large 2θ angles, where the peaks from Cu Kα_1 and Cu Kα_2 could be distinguished. Complete three-dimensional intensity data (3271 nonequivalent reflections to the limit $2\theta = 164°$ for the Cu sphere) were measured on a GE XRD5 diffractometer by the stationary crystal-stationary counter method using a 5° take-off angle. Balanced Ni–Co Ross filters were used for monochromatization. The intensities of 333 reflections were less than twice the background values in that ($\sin\theta/\lambda$) range and were given zero weight during the refinement. The crystals used for the data collection were mounted with the b^* axis along with the ϕ axis of the goniostat and had the dimensions 0.3 × 0.2 × 0.2 mm. The intensities were corrected for the Lorentz–polarization and α_1–α_2 correction factors. The difference in absorption as a function of ϕ was measured for axial reflections and was used for correcting approximately the anisotropy of absorption.

Determination and Refinement of the Structure. The structure solution was obtained using the heavy-atom method, after the location of the sulfur atoms were obtained from a sharpened three-dimensional Patterson map. The structural parameters were refined by the least-squares method using the block-diagonal approximation to a final R value of 0.049. Blocks of (9 × 9) were used for all non-hydrogen atoms with individual anisotropic thermal parameters. Hydrogen atoms were located from electron-density difference maps and their positional and individual thermal parameters were refined using blocks of (4 × 4). The scattering factors and anomalous dispersion corrections for S, O, N, and C given by Cromer and Lieberman[20a] were used. For the hydrogen atoms the values given by Stewart, Davidson, and Simpson[20b] were used. The differential synthesis weighting scheme with $w = 1/f_N$, where f_N is the scattering factor of nitrogen atom, was used for the refinement.

The absolute configuration was determined using the anomalous dispersion effects of the S (O, N, and C) atoms for the Cu Kα radiation, using the R-factor method[21] and is shown in Figure 1. The numbering of these atoms has been made to agree with chemical nomenclature for easy comparison. The ratio of the R factors for the coordinates of the structure shown in Figure 1 and of its mirror image was 0.96, establishing that the structure given in Figure 1 is in the correct absolute configuration.

B. NMR Spectroscopy. Proton magnetic resonance spectra were obtained on Varian A60A, Varian XL-100, and Varian HR-220 spectrometers in the continuous wave mode (CW). ^{1}H relaxation time measurements were determined on the Varian XL-100 spectrometer by the inversion recovery method using the 180°–τ–90° sequence. ^{13}C spectra were determined on Varian XL-100 operating in the Fourier transform (FT) mode. The spectral width was 5 kHz with a proton decoupler bandwidth of 5.5 kHz. Sample tubes with 10-mm outer diameter were employed, and the compound was dissolved in 10–15% (w/v) Me_2SO-d_6. Sample temperatures were 23 and 100 °C, respectively.

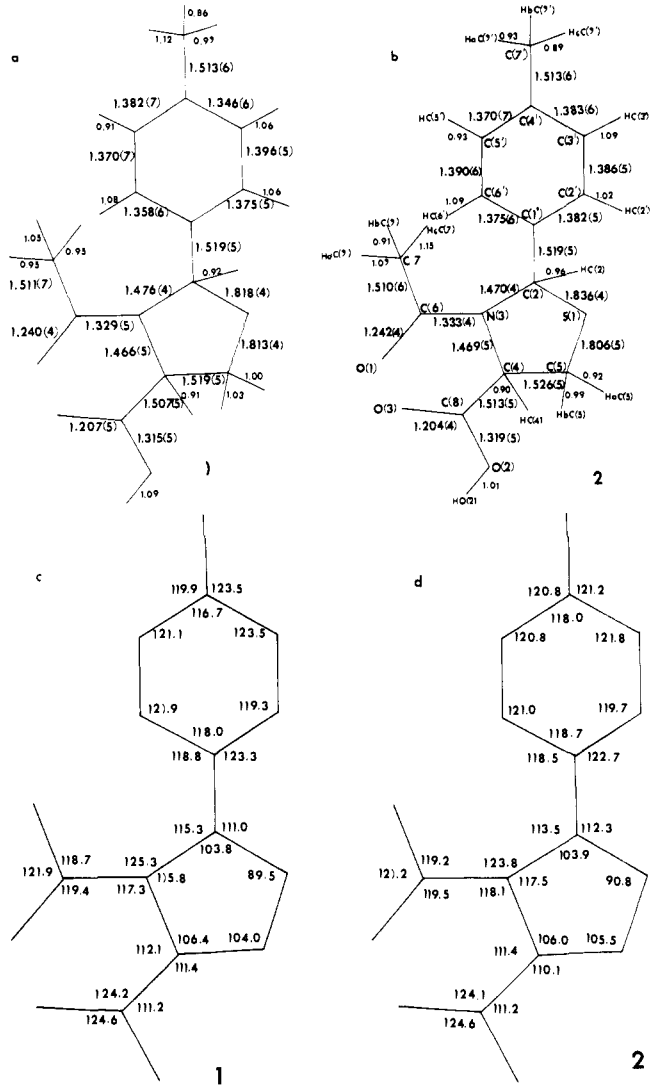


Figure 2. Bond distances (a) of molecule 1 and (b) of molecule 2; bond angles (c) of molecule 1 and (d) of molecule 2. The prefix 2 in labeling the atoms of molecule 2 as in coordinate tables is dropped for convenience.

Discussion of the Structure from X-Ray Crystallography

The final positional and thermal parameters for non-hydrogen atoms are given in Table I and those for hydrogen atoms in Table II. The observed and calculated structure factors will be deposited (see paragraph at end of paper regarding supplementary material). Figures 1a and 1b illustrate the stereochemistry of the molecule. Bond distances and angles involving the hydrogen atoms fall in the usual range for x-ray determinations and are given in Figure 2. The average esd's in the bond distances are 0.004 Å for S–C bonds, 0.005 Å for C–O bonds, and 0.006 Å for C–N and C–C bonds. The average esd in bond angles not involving a hydrogen atom is 0.4°.

A. Bond Distances and Angles. There are two independent molecules in the asymmetric unit of the crystal. Though the two molecules differ conformationally, the bond distances and angles in the two molecules agree with each other very well except in a few cases. The C(3′)–C(4′) bond differs by as much as 0.037 Å, and the C(5′)–C(6′) and C(2)–S bonds differ by 0.020 and 0.018 Å, respectively. These differences are larger than three times the corresponding standard deviations. In view

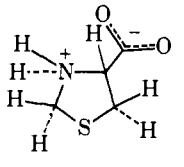
Table I. Atomic Coordinates and Thermal Parameters ($\times 10^4$)[a]

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
				(a) Molecule 1					
S	25841 (6)	0000	35223 (8)	41 (4)	234 (2)	80 (1)	30 (2)	38 (1)	67 (3)
O(1)	4713 (2)	1783 (4)	1091 (2)	32 (1)	258 (7)	95 (3)	−51 (5)	12 (3)	106 (7)
O(2)	4592 (2)	−2103 (4)	802 (3)	47 (1)	209 (7)	97 (3)	47 (5)	17 (3)	−71 (7)
O(3)	3503 (2)	−785 (5)	−313 (3)	50 (2)	351 (10)	86 (3)	85 (6)	−24 (3)	−138 (8)
N(3)	3451 (2)	1232 (4)	1821 (2)	26 (1)	137 (5)	67 (2)	−16 (4)	6 (3)	−24 (6)
C(2)	2675 (2)	1647 (5)	2444 (3)	34 (1)	157 (7)	65 (3)	15 (6)	5 (3)	−36 (7)
C(4)	3723 (2)	−458 (5)	1908 (3)	25 (1)	139 (7)	75 (3)	−16 (5)	7 (3)	25 (7)
C(5)	2978 (3)	−1368 (6)	2407 (4)	36 (2)	157 (8)	115 (4)	−27 (6)	19 (4)	13 (10)
C(6)	4017 (2)	2280 (6)	1437 (3)	39 (2)	171 (8)	74 (3)	−44 (3)	−15 (4)	48 (8)
C(7)	3794 (3)	4048 (7)	1451 (5)	69 (3)	168 (9)	143 (5)	−50 (9)	−26 (6)	85 (12)
C(8)	3918 (2)	−1116 (6)	669 (3)	33 (2)	190 (8)	82 (3)	−22 (6)	7 (4)	−68 (9)
C(1′)	1829 (2)	1863 (6)	1582 (3)	34 (2)	167 (8)	81 (3)	27 (6)	8 (4)	−21 (8)
C(2′)	1752 (2)	1503 (7)	338 (3)	33 (2)	255 (11)	72 (3)	36 (7)	−2 (3)	−21 (10)
C(3′)	931 (3)	1613 (8)	−363 (4)	42 (2)	299 (13)	90 (4)	56 (9)	−12 (4)	−45 (12)
C(4′)	202 (3)	2074 (8)	129 (4)	38 (2)	306 (14)	116 (4)	63 (9)	−11 (5)	17 (14)
C(5′)	299 (3)	2469 (11)	1379 (5)	47 (2)	539 (22)	126 (5)	187 (13)	24 (6)	−34 (19)
C(6′)	1100 (3)	2383 (9)	2073 (4)	56 (2)	403 (17)	97 (4)	157 (11)	12 (5)	−45 (14)
C(7′)	−692 (3)	2175 (11)	−623 (5)	39 (2)	478 (20)	186 (7)	76 (13)	−40 (6)	−78 (22)
				(b) Molecule 2					
2S	24230 (7)	−49828 (21)	83044 (9)	47 (1)	249 (2)	82 (1)	37 (2)	49 (1)	67 (3)
2O(1)	4822 (2)	−3725 (4)	6051 (2)	27 (1)	153 (5)	93 (2)	−1 (4)	16 (2)	47 (6)
2O(2)	4531 (2)	−7497 (4)	5868 (2)	52 (1)	147 (5)	92 (3)	44 (5)	22 (3)	−5 (6)
2O(3)	3521 (2)	−6057 (4)	4698 (2)	51 (1)	222 (7)	76 (2)	55 (5)	−21 (3)	−84 (7)
2N(3)	3547 (2)	−3978 (4)	6830 (2)	24 (1)	117 (5)	71 (2)	4 (4)	3 (3)	−23 (6)
2C(2)	2776 (2)	−3334 (5)	7358 (3)	35 (2)	171 (8)	68 (3)	34 (6)	15 (3)	−42 (8)
2C(4)	3693 (2)	−5719 (5)	6920 (3)	29 (1)	125 (6)	71 (3)	−12 (5)	3 (3)	4 (7)
2C(5)	2840 (3)	−6437 (6)	7280 (4)	41 (2)	166 (8)	116 (4)	−18 (7)	32 (5)	27 (10)
2C(6)	4174 (2)	−3069 (5)	6429 (3)	29 (1)	126 (6)	72 (3)	−4 (5)	−13 (3)	28 (7)
2C(7)	4074 (3)	−1265 (6)	6426 (4)	44 (2)	130 (7)	126 (5)	−0 (6)	−17 (5)	28 (10)
2C(8)	3901 (2)	−6415 (5)	5696 (3)	33 (1)	121 (6)	84 (3)	−12 (5)	11 (3)	−28 (8)
2C(1′)	2055 (2)	−2760 (5)	6385 (3)	30 (1)	141 (7)	84 (3)	5 (5)	21 (3)	−0 (8)
2C(2′)	1892 (2)	−3469 (5)	5228 (3)	27 (1)	150 (7)	90 (3)	16 (5)	6 (3)	−18 (8)
2C(3′)	1189 (3)	−2954 (6)	4404 (4)	35 (2)	194 (9)	102 (4)	20 (7)	−11 (4)	4 (10)
2C(4′)	639 (2)	−1733 (7)	4706 (4)	30 (2)	216 (10)	133 (5)	30 (7)	13 (5)	47 (12)
2C(5′)	815 (3)	−1019 (7)	5850 (4)	47 (2)	250 (12)	139 (5)	119 (9)	34 (5)	−10 (13)
2C(6′)	1516 (3)	−1529 (7)	6685 (4)	43 (2)	231 (10)	108 (4)	72 (8)	29 (5)	−48 (11)
2C(7′)	−111 (4)	−1158 (10)	3782 (5)	62 (3)	348 (17)	183 (7)	140 (3)	−53 (8)	−36 (20)

[a] TF = [exp $(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)$].

of the good overall agreement between the two molecules, the differences in the C(3′)–C(4′), C(5′)–C(6′), and C(2)–S bonds of the two molecules do not seem to be artifacts, but real, though the reason for such differences is not clear.

No accurate crystal structure studies on thiazolidine rings seem to have been carried out before our work was started. During the progress of our work, reports of the study of thiazolidine-4-carboxylic acid III by two groups, one using photographic techniques[15] and the other using diffractometer,[16] appeared. More recently the structurally related 2-imino-4-oxo-1,3-thiazolidine hydrochloride has been studied by photographic techniques.[17] In view of the inaccuracies inherent in the photographic techniques, we shall compare our results only with those obtained on thiazolidine-4-carboxylic acid (III) using diffractometer data.[16] Thiazolidine-4-carboxylic acid (III) crystallizes as a zwitterion whereas the N-acetylation of



III

2-tolylthiazolidinecarboxylic acid prevents the molecule from taking up such a zwitterionic structure. A comparison of the bond distances and angles (Table III) clearly brings out the chemical differences between the two molecules. In the zwitterionic form, N(3) has sp^3 hybridization whereas in II, it has sp^2 hybridization. This change in hybridization causes an increase of the N–C distances in the zwitterionic form compared with the neutral molecule (II). Also, the ring angle at N(3) is smaller in the zwitterionic form by 5.5 and 7.2° as compared with the molecules 1 and 2 of II. The dimensions of the carboxylic acid group in II lies in the usual range of values found in amino acids and dicarboxylic acids. But the C(sp^3)–C(sp^2) bond in thiazolidine-4-carboxylic acid (which corresponds to the C(4)–C(8) bond in II) is unusually long, longer than the C(sp^3)–C(sp^3) bond length of 1.54 Å. The two S–C bonds in molecule 1 of II are nearly equal, in molecule 2 of II, they are slightly unequal, and in thiazolidine-4-carboxylic acid, they are very unequal; the ring angle at S has remained practically the same in these three molecules.

B. Conformation of Thiazolidine Rings. Since thiazolidine is a five-membered ring, it can, in principle, undergo pseudorotation like cyclopentane,[22-24] but the introduction of the heteroatoms, substituents, and especially the sp^2-hybridized N will introduce a potential energy barrier restricting any pseudorotation. Since there is not sufficient x-ray diffraction data on these rings and since our x-ray and NMR results share a "locked in" conformation for II, we have used a simple description of the conformation in the following discussions, rather than the more sophisticated analysis of Cremer and Pople.[24]

Table II. Atomic Coordinates ($\times 10^3$)

	x	y	z
	(a) Molecule 1		
H(2)	275 (2)	249 (4)	297 (3)
H(4)	422 (2)	−59 (4)	246 (3)
AH(5)	244 (2)	−142 (6)	185 (3)
BH(5)	320 (3)	−234 (6)	290 (4)
AH(7)	424 (3)	457 (6)	101 (4)
BH (7)	318 (3)	427 (7)	100 (4)
CH(7)	379 (3)	447 (8)	232 (5)
H(2′)	226 (3)	92 (6)	−8 (4)
H(3′)	84 (3)	122 (6)	−131 (3)
H(5′)	−23 (3)	259 (6)	166 (4)
H(6′)	107 (3)	279 (7)	300 (4)
AH(7′)	−111 (4)	106 (9)	−48 (5)
BH(7′)	−111 (3)	268 (7)	−37 (4)
CH(7′)	−75 (3)	154 (7)	−141 (4)
HO(1)	481 (4)	−262 (9)	−6 (6)
	(b) Molecule 2		
2H(2)	292 (2)	−265 (5)	802 (3)
2H(4)	415 (3)	−599 (5)	748 (3)
2AH(5)	238 (3)	−635 (6)	668 (3)
2BH(5)	292 (3)	−749 (6)	766 (3)
2AH(7)	459 (3)	−72 (6)	604 (4)
2BH(7)	358 (3)	−94 (7)	596 (4)
2CH(7)	403 (3)	−101 (8)	742 (4)
2H(2′)	226 (2)	−443 (5)	500 (3)
2H(3′)	105 (2)	−363 (5)	354 (3)
2H(5′)	50 (3)	−17 (7)	615 (4)
2H(6′)	160 (3)	−99 (7)	761 (4)
2AH(7′)	−33 (3)	−17 (9)	404 (4)
2BH(7′)	−63 (4)	−233 (10)	383 (5)
2CH(7′)	−2 (3)	−178 (9)	312 (5)
2HO(1)	470 (3)	796 (8)	509 (5)

Table III. Comparison of the Bond Distances (Å) and Bond Angles (deg) of II with Thiazolidine-4-carboxylic Acid (III)[a]

	Molecule 1	Molecule 2	III
	Bond distances		
S(1)-C(2)	1.818	1.836	1.770
S(1)-C(5)	1.813	1.806	1.828
C(2)-N(3)	1.476	1.470	1.521
N(3)-C(4)	1.466	1.469	1.486
C(4)-C(5)	1.519	1.526	1.525
C(4)-C(8)	1.507	1.513	1.569
C(8)-O(2)	1.315	1.319	1.248
C(8)-O(3)	1.207	1.204	1.240
	Bond angles		
C(5)-S(1)-C(2)	89.5	90.8	89.4
S(1)-C(2)-N(3)	103.8	103.9	107.0
C(2)-N(3)-C(4)	115.8	117.5	110.3
N(3)-C(4)-C(5)	106.4	106.0	109.2
C(4)-C(5)-S(1)	104.0	105.5	102.8
N(3)-C(4)-C(8)	112.1	111.4	109.0
C(5)-C(4)-C(8)	111.4	110.1	110.8

[a] The numbering of atoms of TC has been altered to correspond with the nomenclature of II. The average esd's of the bond distances and angles in III are 0.008 Å and 0.4° compared with 0.005 Å and 0.4° for II.

Table IV. Torsion Angles (deg) in II and Thiazolidine-4-carboxylic Acid (III)

	Molecule 1	Molecule 2	III
C(5)-S(1)-C(2)-N(3)	−34.8	−29.8	36.9
S(1)-C(2)-N(3)-C(4)	18.7	13.8	−20.5
C(2)-N(3)-C(4)-C(5)	11.9	13.8	−11.7
N(3)-C(4)-C(5)-S(1)	−37.1	−35.3	37.3
C(4)-C(5)-S(1)-C(2)	42.3	38.4	−42.6
S(1)-C(2)-C(1′)-C(2′)	−109.8	−85.8	
C(2)-N(3)-C(6)-O(1)	169.5	176.6	
N(3)-C(4)-C(8)-O(2)	142.4	139.1	−169.4

The best plane through four of the five ring atoms omits the sulfur for both molecules 1 and 2 in II. The equation to this plane is $0.4221X + 0.0932Y + 0.9017Z = 4.0647$ for molecule 1 and $-0.3416X + 0.0149Y + 0.9397Z = 8.4957$ for molecule 2; the direction cosines are with respect to *a*, *b*, and *c** axes, and *X*, *Y*, *Z* are in Å. The sulfur atom deviates by −0.841 Å for molecule 1 and −0.753 Å for molecule 2 to the side of the plane (exo) opposite to the carbonyl group. In thiazolidine-4-carboxylic acid, the sulfur atom deviates by 0.843 Å from the best plane, but endo to the carboxyl group. The torsion angle around the ring is given in Table IV along with those of thiazolidine-4-carboxylic acid. From a comparison of these torsion angles several important conclusions emerge: (i) Molecules 1 and 2 are similar in their overall conformation, but differ somewhat in detail. Molecule 2 is somewhat less puckered than molecule 1. (ii) The pucker of the molecules of II is enantiomeric to that of thiazolidine-4-carboxylic acid. (iii) Since none of the torsion angles around the bonds in the ring is near zero, the molecules are not in an envelope conformation, but take up a "twist" S-exo-C(5)-endo conformation. In 1,3-thiazolidines, conformations close to envelopes have been proposed from NMR data.[13] (iv) The change in hybridization of N from sp^3 in thiazolidine-4-carboxylic acid to sp^2 of II has not resulted in any flattening of the ring, contrary to the suggestion of other workers.[16,25] The p*K* of the thiazolidine ring ($pK_a = 6.24$) compared with that of the pyrrolidine rings in prolines ($pK_a = 10.60$) was explained[3,25] on the basis of an expected flattening of the ring. Our results show that though the ring angle at N changed from 110.3° to 115.8° (for molecule 1) and to 117.5° (for molecule 2) on going from sp^3 to sp^2 hybridization, the ring angles at other atoms changed (except at S which did not change) in such a way to maintain the pucker (the sum of the ring angles in thiazolidine-4-carboxylic acid, molecule 1 and 2 of II are respectively, 519.2, 519.5, and 523.7°).

C. Stereochemistry of the Molecule. The 2-tolyl substituent is cis to the 4-carboxyl group (Figure 3). The absolute configuration of the molecule as determined by the anomalous dispersion technique is 2*R*,4*R* using the standard conventions for depicting chirality. We also examined the crystals analogous to that of II, but obtained from D-cysteine. These crystals had unit cell dimensions and intensity profiles (neglecting anomalous dispersion effects) along the axes identical with that of II. Consequently, the absolute configuration of these crystals must be 2*S*,4*S*, in agreement with expectation from chemical behavior identical with that of II.

The keto oxygen of the *N*-acetyl group is trans to C(2) in both the molecules; the N(3)-C(6) torsion angles are 169.5° for molecule 1 and 176.6° for molecule 2. The largest difference between molecules 1 and 2 rests in the orientation of the phenyl group; the torsion angles S-C(2)-C(1′)-C(2′) for the molecules 1 and 2 are, respectively, −109.8 and −85.8°. The C(8)-O(3) bond of the carboxyl group is synplanar to C(4)-N(3) with the torsion angles of −38.1 and −43.0° for molecules 1 and 2. In thiazolidine-4-carboxylic acid, the corresponding torsion angle calculated by us is 14.5°. This synplanar orientation of the C=O bond with respect to C-N bond has been noticed and commented upon by several investigators working on the conformation of amino acids and peptides.

D. Hydrogen Bonding and Packing. The hydroxyl OH of molecule 1 is strongly (as judged by the distances) hydrogen

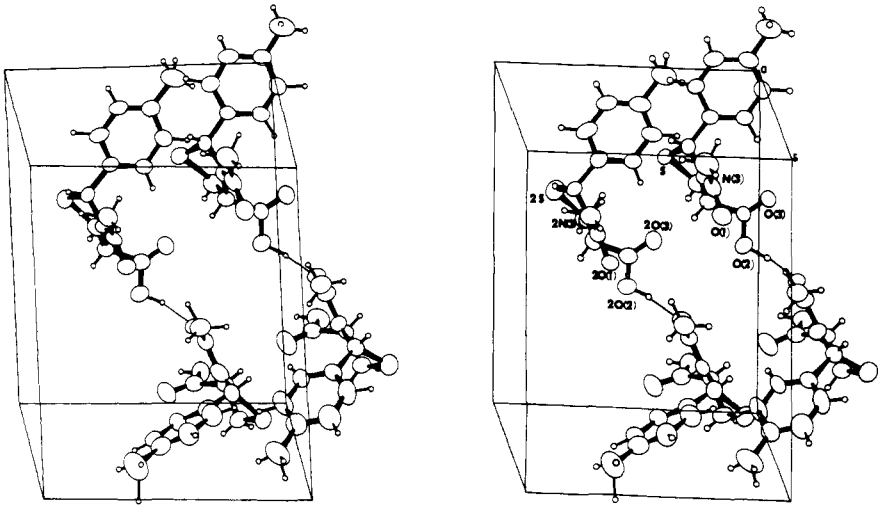
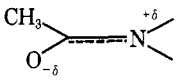


Figure 3. A stereoview of the packing and hydrogen bonding.

Table V. Hydrogen Bonding

D-H···A	D···A	D-H	H···A	D-H···A	Trans	Eq pos
O(2)-HO(2)···O(1)	2.585 (4) Å	1.09 (7) Å	1.52 (7) Å	167 (2)°	$\bar{1}10$	$\bar{x}, \frac{1}{2}+y, \bar{z}$
2O(2)-2HO(2)···2O(1)	2.605 (4)	1.01 (6)	1.60 (6)	170 ((4)	$1\bar{1}1$	$\bar{x}, \frac{1}{2}+y, \bar{z}$

bonded to the keto oxygen of the acetyl group rather than to the carboxyl group of another molecule 1 (see Figure 3 and Table V), and similarly molecule 2 is hydrogen bonded to another symmetry-related molecule 2. The reason for the participation of O(1) rather than O(3) may be due to the predominant contribution of the resonance form IV which endows



IV

O(1) with a partial negative charge, making it a good H bond acceptor.

The molecules pack in such a way that there is not any contact between one molecule to another except through the hydrogen bonds. The molecules 1 and 2 (except the tolyl rings) are related by approximate relations of the type $x_1 = x_2, y_1 = \frac{1}{2} + y_2, z_1 = -\frac{1}{2} + z_2$.

NMR Spectroscopy

A 220-MHz spectrum of the *N*-acetyl-2-(*p*-tolyl)thiazolidine-4-carboxylic acid (II) at the probe temperature is shown in Figure 4. In this solvent the molecule exists in two conformers in solution; the predominant conformer (a) is 76% as determined from peak area measurements. Of interest in the conformational analysis of the conformers are the proton resonances at C(4) and C(5), which comprise a ABX system. Analysis of this portion of the spectrum is made difficult (and would have been impossible at 100 MHz) by the overlap of the C(5) protons of the minor conformer (b) with one of the C(5) protons (A) of the major conformer. However, since there is adequate separation of the A and B resonances at 220 MHz, first-order analysis could be applied to the ABX system of the major conformer (Figure 5, above) and the results obtained checked by computer simulation (Figure 5, below). In the analysis of the ABX system, the A proton is assumed to resonate at a lower field than the B proton. From the computer simulation an approximate position of the "A" proton has been obtained by trial of several values. The sum of the coupling constants of the minor conformer (b) could be obtained from the separation of the outer lines of the X portion of the spectrum and is 9.7 cps. At 100 °C the spectrum (Figure 6) shows an apparent disappearance of the two separate conformers. However, the positions of the peaks are intermediate between conformers a and b, indicating that those conformers are present even at 100 °C but are equilibrating at a faster rate than at the probe temperature. Since only a 100-MHz spectrum was available at 100 °C a second-order analysis has been carried out on the ABX system in the prescribed manner.[26] Proton shifts and coupling constants are presented in Table VI and have been checked by computer simulation. The values of the three coupling constants are found to be slightly smaller in the averaged spectrum at 100 °C. The NMR spectrum of the unacetylated thiazolidine derivative I (Figure 7) also clearly indicates the presence of two conformers almost equally distributed (56% of the major conformer a). The X portion of the ABX pattern is a quadruplet and is similar for both conformers. Unfortunately the AB protons of both conformers overlap and hence the ABX pattern could not be analyzed.

Spin-lattice relaxation times (T_1) for certain protons have been determined by the inversion recovery method for the two conformers of I, and the results are presented in Table VII.

Proton decoupled ^{13}C spectra were also determined (Table VIII). Assignments were based on selective ^1H decoupling and on off-resonance decoupling. Assignments to the carbonyl carbons (carboxylic acid and *N*-acetyl) are not definite. The carbonyl peak with a minor satellite peak was assumed to be due to the *N*-acetyl carbonyl.

Discussion

Conformation Analysis Using X-Ray and NMR Results. Both the N-acetylated thiazolidine derivative II and the unacetylated compound I exist in two conformations in Me_2SO solution. The two conformers were found to be very stable and exist at 100 °C. In the case of the *N*-acetyl derivative II there is an averaging out of the spectrum, indicating a fast interconversion of the conformers, whereas in I the two conformers could be seen as separate entities at elevated temperatures. Thus, *the existence of the stable conformers does not depend*

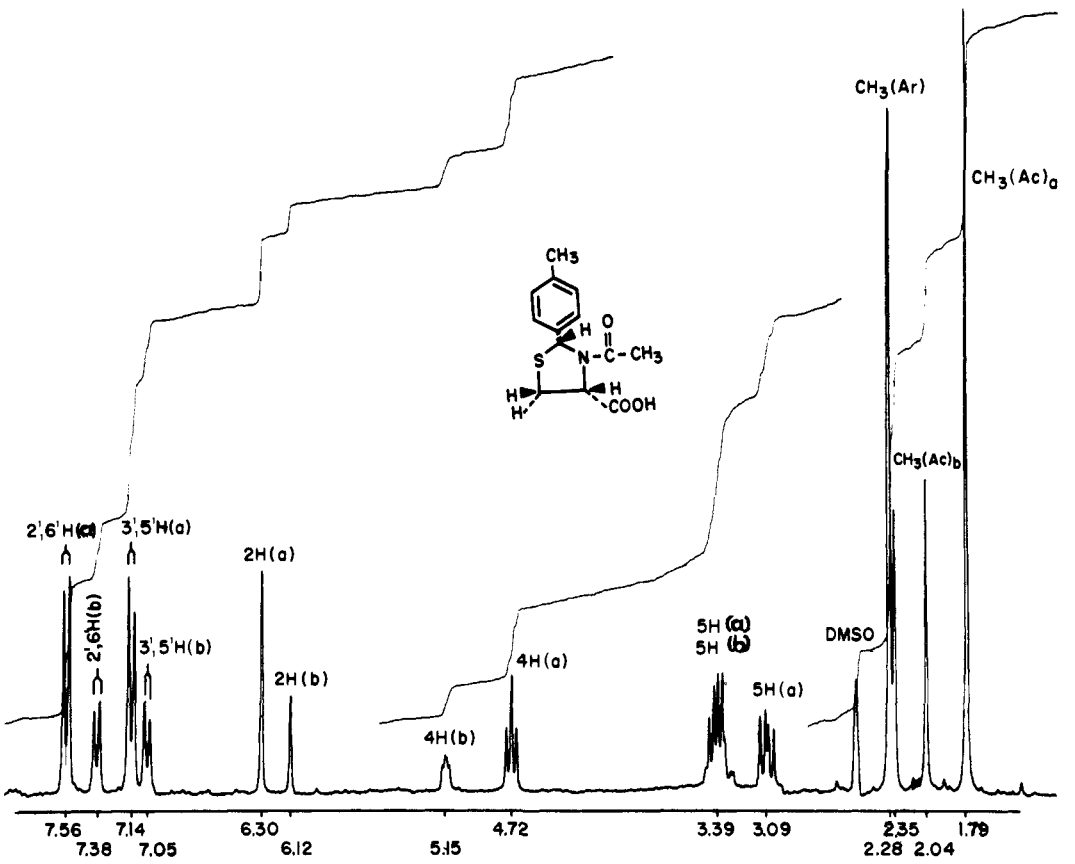


Figure 4. 220-MHz spectrum of the *N*-acetyl-2-(*p*-tolyl)thiazolidine-4-carboxylic acid (II) in Me_2SO-d_6 at probe temperature showing the presence of the major conformer "a" and the minor conformer "b".

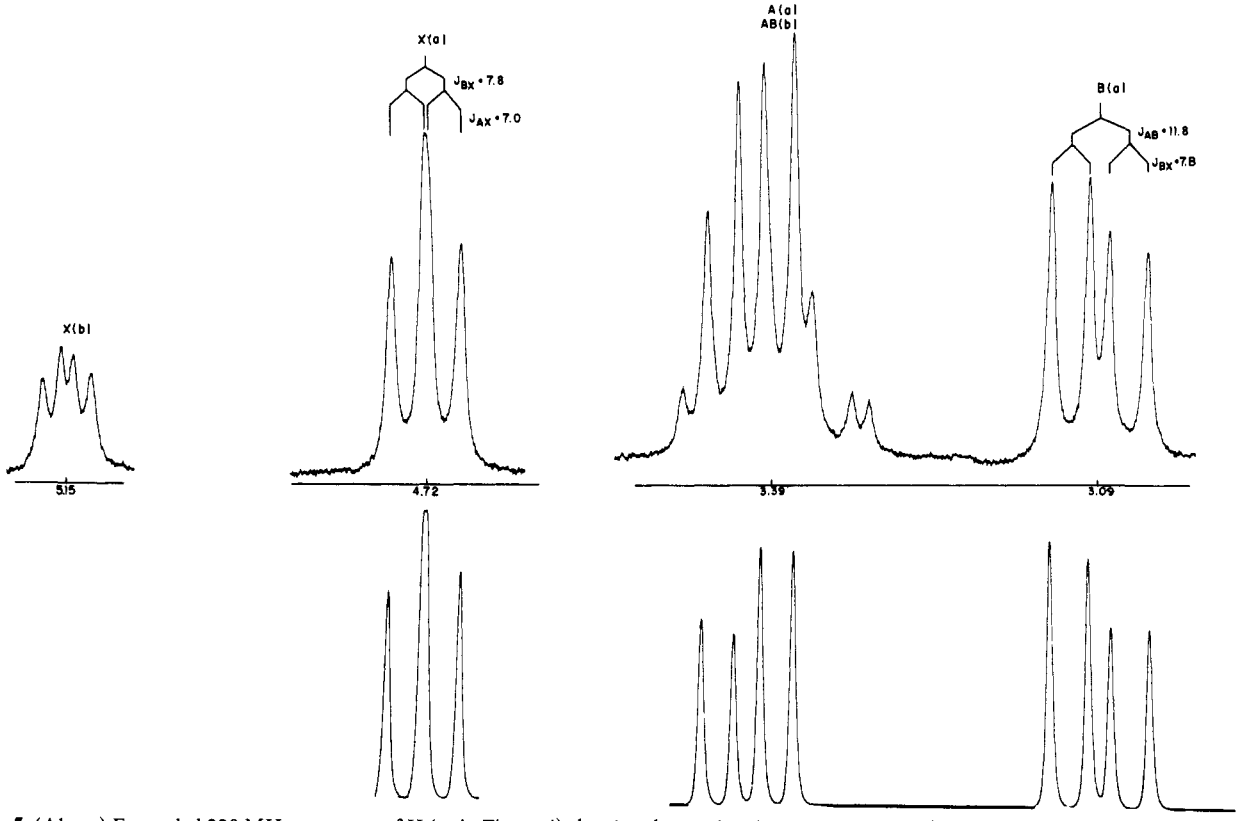


Figure 5. (Above) Expanded 220 MHz spectrum of II (as in Figure 4) showing the overlapping $5H_2$ protons of the two conformers comprising an ABX system for the two conformers. (Below) Calculated ABX spectrum for the major conformer.

on the presence of the N-acetyl as might be expected from earlier work.[27] Although the appearance of the ABX spectrum in both conformers of I is similar to the N-acetylated derivative, we can only assume that this similarity extends to the actual conformations of the two derivatives.

It should be pointed out here that I is almost certainly a

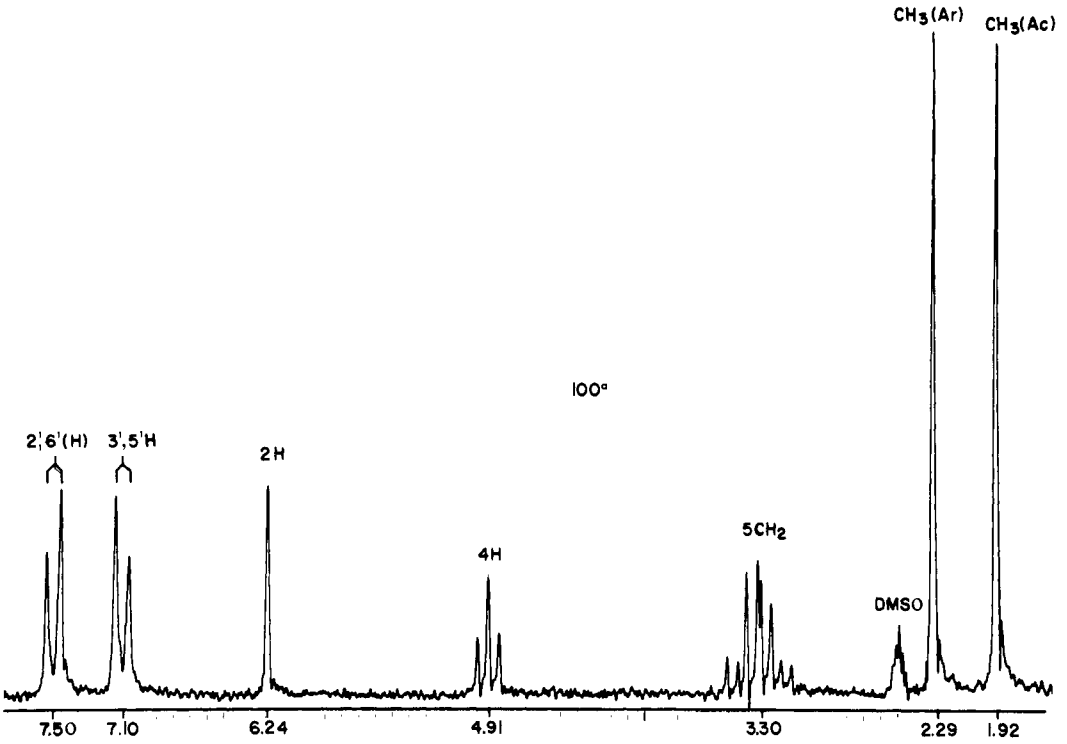


Figure 6. 100-MHz spectrum of II in Me_2SO-d_6 at 100 °C.

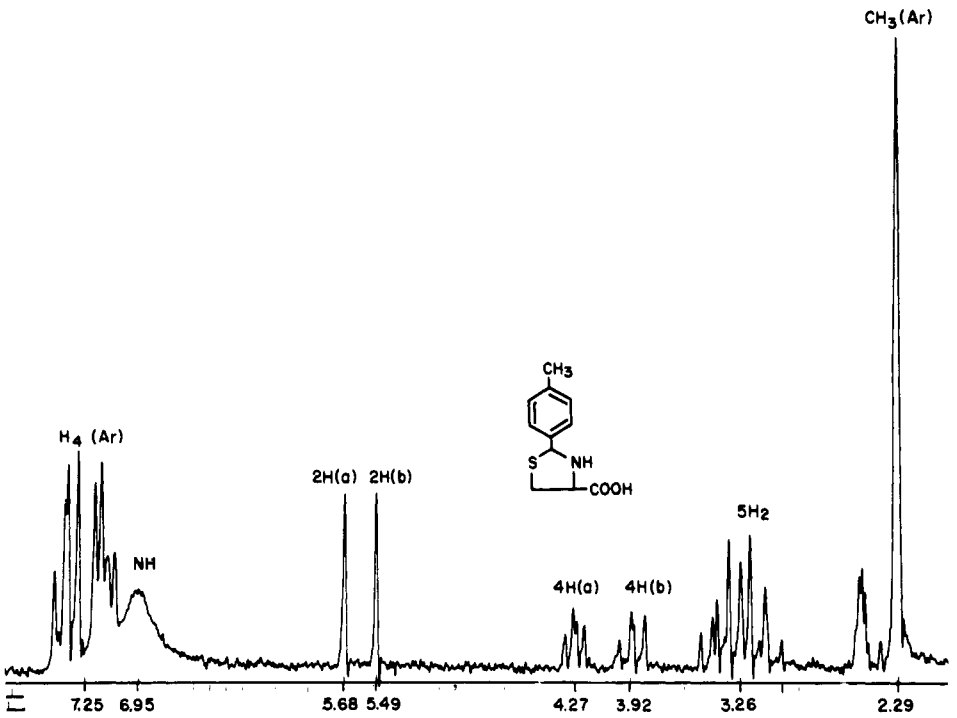


Figure 7. 100-MHz spectrum of I in Me_2SO-d_6 at probe temperature showing the presence of two conformers a and b.

zwitterion. Hence it may appear at first sight that the thiazolidine rings in I and II are not strictly comparable. On the other hand, the results discussed earlier in connection with the conformation of III clearly show (Table IV) that the magnitudes of the pucker of III and II as found by x-ray analysis are remarkably similar, despite the fact that III lacks the 2 substituent, and the two rings have nitrogen atoms with different hybridization. X-ray analysis of II has also shown that except for the intermolecular H bond, there are hardly any contacts of the molecule in the crystal structure. Hence it is likely that the conformers of II as determined by the x-ray crystallography resemble those found in solution.

The geminal coupling constant at C(5) decreases slightly on heating, indicating that this value in conformer b may be of about 11.4 cps. This corresponds to a difference of about 5° in the C(5)-gem dihedral angle,[28] which is in accord with what we find from x-ray work. (The H(4)-C(4)-C(5)-BH(5) torsion angles for molecule 1 and 2 are, respectively, −31 and −35°.) In the conformer b we could determine the $J_{AX} + J_{BX}$ value from the X part of the spectrum as 9.7 cps, but not the coupling constants individually, because of the overlap. This value is appreciably less than that for the major conformer (14.8 cps). Both values average out on heating to 13 cps. Thus a reasonable value for each of the coupling constants for the

Table VI. Proton Shifts and $^1H,^1H$ Coupling Constants of 1,3-Thiazolidine Derivatives in Me_2SO-d_6

Compound	Temp, °C	Conformer	2-CH	4-C-H δ_X	5-CH_2 δ_A	5-CH_2 δ_B	J_{AB}	$J_{AX}+J_{BX}$	J_{AX}	J_{BX}	Tolyl CH_3	*N*-Acetyl CH_3	Aromatic protons
N-Acetyl-2-(*p*-tolyl)-thiazolidine-4-carboxylic acid	28	a (76%)	6.30	4.72	3.40	3.09	−11.8	14.8	7.0	7.8	2.28	1.79	7.14, 7.56
		b (24%)	6.12	5.15	~3.40		~11.4	9.7	~4–5	~4–5	2.25	2.04	7.05, 7.38
	100		6.24	4.91	3.40	3.21	−11.6	13.0	6.9	6.1	2.29	1.92	7.10, 7.50
2-(*p*-Tolyl)-thiazolidine-4-carboxylic acid	28	a (56%)	5.68	4.27	~3.32						2.29		~7.25
		b (44%)	5.49	3.92	~3.32						2.29		~7.25

Table VII. Relaxation Times (T_1) in Seconds

Compound	Conformer	2-CH	4-CH	Tolyl CH_3	*N*-Acetyl CH_3	Aromatic protons
N-Acetyl-2-(*p*-tolyl)-thiazolidine-4-carboxylic acid	a	0.56	0.60	0.39	0.40	0.63
	b	0.57	0.49		0.47	

Table VIII. ^{13}C Chemical Shifts in ppm of *N*-Acetyl-2-(*p*-tolyl)-(*R*)-thiazolidine-4-carboxylic Acid in Me_2SO-d_6 Solution at 23 and 100 °C[a]

Temp, °C	Conformer	C(2)	C(4)	C(5)	C(1′)	C(2′,6′)	C(3′,5′)	C(4′)	C(7′)	Me (acetyl)	C=O (acetyl)	C=O (acid)
23	a (70%)	65.6	64.4	31.7	137.2	126.4	129.2	139.0	20.8	22.5	171.4	169.2
	b (30%)	66.2	64.1	33.7	136.6	126.7	128.6	137.9	20.8	23.3	172.0	169.2
100	a + b	66.1	64.3	32.6	137.0	126.7	128.8	138.5	20.6	22.5	171.2	169.2

[a] Me_2SO-d_6 taken as internal standard at 39.6 ppm.

minor conformer is expected to be 4–5 cps. If Karplus relationship is maintained, a decrease in the sum of coupling constants is expected from the dihedral angles in the conformer "b" as determined by x-ray crystallography. Thus the conformer with small J values corresponds most closely to the conformer with the larger H(4)-C(4)-C(5)-BH(5) dihedral angle.

We hoped to obtain some information regarding the stereochemical relationships by ^1H-relaxation time T_1 determinations. The primary mechanism of relaxation in protons is the dipole-dipole interactions, particularly with the neighboring protons, and this has been shown to be useful in conformational studies of carbohydrates.[29] Since no significant differences were found in the relaxation times of the resolvable protons in both conformers (Table VII), differences in the dihedral angles of the two conformers must be small.

The proton decoupled ^{13}C spectra also indicate existence of the two conformers in about the same proportion as shown by the ^1H spectra (Table VII). The most significant feature of the ^{13}C probe-temperature spectrum is the downfield displacement of the C(5) (by 2 ppm) and C(2) resonances (by 0.6 ppm) and the slight upfield displacement of the C(4) resonances (by 0.4 ppm) in the minor conformer with respect to the major conformer. Thus, the two ring carbon atoms which are involved in the conformational change have most pronounced shifts. The downfield displacement of the C(5) carbon may be due to the relief of the Pitzer strain, which is due to the increased staggering of C(4) and C(5) protons in the minor conformer.

Thus, the NMR spectroscopy is consistent with the existence of two very stable conformers which are probably similar to those found in the crystal.

Goodman et al.[27] have observed two conformers in their studies on the N-acetylated thiazolidines and have postulated that they are derived from two isomers due to the restricted rotation of the *N*-acetyl group. Similar observations have been made more recently on N-formylated thiazolidine derivatives.[14] It should be pointed out that these derivatives have either two methyl groups or two hydrogens as substituents on the C(2) and C(4) positions and hence are not strictly comparable with our compounds. In these cases differences in conformations have been attributed to differences in geometry around the carbon–nitrogen bond, and an envelope conformation with the nitrogen as a flap atom has been proposed for other 2-substituted 1,3-thiazolidines.[13] In the latter study the two conformers could not be detected, presumably because of the choice of relatively nonpolar solvents ($CDCl_3$ or benzene-d_6 were used). It appears that Me_2SO and other very polar solvents have the property of slowing down the rate of the interconversion of conformers to the extent that they can be observed by NMR. It was concluded in this study[13] that the envelope conformers exist as a number of pseudorotamers which are readily interconvertible because of small energy differences between them.

Our results indicate that the thiazolidine derivatives I and II exist as two very stable conformers in the solid and probably in solution and this result is inconsistent with the existence of any pseudorotamers. In the solid, the two stable conformers are best described as being in the twist conformation, in which S and C(5) atoms are displaced in opposite directions by −0.56 and 0.30 Å in one conformer and by −0.42 and 0.35 Å in another. The plane through the C(2)-N(3)-C(4) [and C(6)] segment for reference is due to the sp^2 nature of N(3). If S or C(5) is in the plane through C(2), N(3), and C(4), then an envelope conformation is generated. If both S and C(5) are displaced from this reference plane, the twist conformation is produced. In this conformation two forms of pucker, enantiomeric to one another, can occur as pointed out already. The

nature of this pucker will be influenced by the substituents on the thiazolidine ring. It is possible that the rotation around the C(2)-C(1′) bond of the tolyl group, which is significantly different in the two conformers of II, may correlate to the degree of puckering and stability of the two conformers, as indicated by the following arguments.

Whatever be the conformation of the thiazolidine ring, the rotation of the tolyl about the C(2)-C(1′) bond will bring the ortho hydrogens at distances of approximately 2.6 Å from the sulfur (as determined from Dreiding models), less than 3.05 Å which is the sum of the van der Waals radii (S = 1.85 Å, H = 1.2 Å) of the contacting atoms. The introduction of the acetyl group and its orientation will present additional steric constraints to the rotation of the tolyl group and to any pseudorotation of the thiazolidine ring. If the keto oxygen of the acetyl is trans to C(2), the tolyl cannot be pseudoequatorial but must be pseudoaxial due to short methyl tolyl contacts. This axial orientation of the tolyl is found in the crystal structure of II. An envelope conformation with S out of the plane of the other four atoms is not energetically favorable since both the tolyl and the carboxyl groups will be axial and will be too near to each other. The steric strain between the axial substituents will be minimized by the "twist" conformation with S and C(5) moving exo and endo, respectively, to the carboxyl. From similar considerations, it can be seen with Dreiding models that the cis conformation of the acetyl will orient the carboxyl axial, and the thiazolidine ring is likely to have the S-endo-C(5)-exo "twist" conformation. Though there seems to be some inherent rigidity of this heterocycle as seen from the conformational similarity of substituted (II) to *un*substituted (III) derivatives (see Table IV), the "freezing out" of conformations in our compounds seems to be due to the nature and number of the substituents.[30] It is quite likely that some of the "frozen out" conformations are separated by high steric barriers, and the conformers observed by NMR with high coalescence temperature may actually be two of these "frozen out" conformers. The NMR data are consistent with the structures of the two conformers, as determined by crystallography, in particular with the conformations of the thiazolidine ring. The two conformers seen by NMR and the two seen by crystallography may have similar ring conformations but different orientation of the tolyl group. We cannot completely rule out that the conformers seen by NMR actually arise due to *N*-acetyl rotation. But the facts that I without the *N*-acetyl also has two stable conformers and that the *N*-acetyl rotation in II will involve major conformational changes in the thiazolidine ring indicate that there are difficulties in invoking the *N*-acetyl rotation in our 2-substituted thiazolidines for explaining the two conformers observed by NMR.

Biochemical Implications

Since the interaction of *p*-tolualdehyde with L-cysteine can be regarded as a model for interaction of pyridoxal phosphate with L-cysteine, this study is of considerable interest with regard to the geometry of the active center in enzymes dependent on this cofactor in general, and to β-lyases in particular.[31] Since the reaction of cysteine with *p*-tolualdehyde gives rise to only *one* configuration of the resulting thiazolidine derivative in which the C(4)-carboxylic acid group is cis to the tolyl group, we are dealing with a reaction of considerable stereospecificity. It could be assumed that other aromatic aldehydes, including pyridoxal and its phosphate, react with cysteine or penicillamine with similar degree of specificity, although bulky groups ortho to the aldehyde (as in pyridoxal phosphate) may have a different, as yet, undetermined effect. The reactions of cysteine with pyridoxal phosphate containing enzymes are thought to proceed first with the formation of an aldimine to which the SH group is subsequently added to form the thiazolidine ring. If the orientation of SH group is unfavorable (e.g., cis to α-H of cysteine), a substitution reaction will occur.[32] In this connection it would be of great interest to determine whether the stereochemistry and the degree of stereospecificity of pyridoxal phosphate with cysteine approaches the analogous condensation with *p*-tolualdehyde. It should be pointed out that Bergel and Harrap[32] based on their kinetic studies have postulated a reverse order of formation of thiazolidine, i.e., an initial addition of the SH group to the aldehyde followed by the ring closure. Subsequently it has been shown that in the condensation of L-cysteine and formaldehyde the order of addition is determined by pH.[25] It is probable that the stereochemistry of the thiazolidine ring formation is determined by the order of addition as well as steric factors yet to be determined.

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Supplementary Material Available: A listing of observed and calculated structure factor magnitudes (21 pages). Ordering information is given on any current masthead page.

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Single-Atom Peri-Bridged Naphthalenes. 2. Synthesis, Crystal Structure, and Reactions of Naphtho[1,8-*bc*]thiete Derivatives

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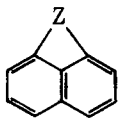
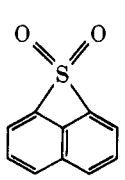
Abstract: Naphtho[1,8-*bc*]thiete (**5**) was prepared in high yield by ultraviolet irradiation of naphtho[1,8-*cd*]1,2-dithiole 1,1-dioxide (**7**). Peracid oxidation of **5** gave the corresponding sulfoxide (**6**) and sulfone (**1**); methylation of **1** gave sulfonium salt (**20**). The x-ray crystal structure of **1** shows a planar naphthalene ring with a compressed C(1)–C(8) peri-carbon distance (2.22 Å). The reactions of **5** and its derivatives with lithium aluminum hydride and other nucleophiles were studied. These reactions generally result in cleavage of the four-membered ring by attack of the nucleophile at the sulfur atom.

Single-atom peri-bridged naphthalenes (I) are compounds in which the 1- and 8-carbon atoms of a naphthalene ring are



I

bonded to a single atom in a bridging group (Z), forming a four-membered ring. These compounds are of interest for a number of reasons, including the expected distortion of the bond lengths and angles of the naphthalene ring and the possibly enhanced tendency of the four-membered ring to undergo ring-opening reactions. The first description of this type of compound appeared in 1965, when Hoffmann and Sieber published the synthesis of naphtho[1,8-*bc*]thiete 1,1-dioxide (**1**).[1] Since that time, numerous attempts to synthesize the carbon-bridged (**2**),[2] nitrogen-bridged (**3**),[3] and oxygen-bridged (**4**)[4] analogues have been unsuccessful. The failure of



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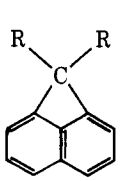

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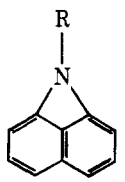

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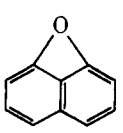

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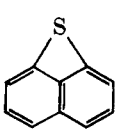

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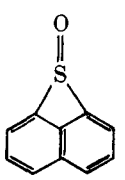
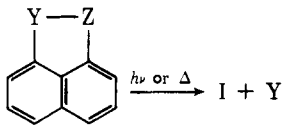


6

many of these approaches may be attributed in part to the strain expected for compounds of this general structure. Nevertheless, an ingenious synthesis of **2** (R = H) was achieved by Bailey and Shechter[5] and we reported the efficient synthesis of naphtho[1,8-*bc*]thiete (**5**), naphtho[1,8-*bc*]thiete 1-oxide (**6**), and naphtho[1,8-*bc*]thiete 1,1-dioxide (**1**) at about the same time.[6] Herein we describe more fully the preparation of **5** and its derivatives, the x-ray crystal structure of **1**, and some interesting reactions of these sulfur-bridged naphthalenes.

A compound of the general structure II, in which the peri



II

positions of a naphthalene ring have been joined by the potential bridging group Z and a leaving group Y, might serve as a synthetic precursor to single-atom peri-bridged naphthalene I. Ideally Y should correspond to a stable fragment, such as nitrogen, sulfur dioxide, carbon dioxide, or carbon monoxide, which is capable of irreversible departure. Photolysis or pyrolysis of II might then lead to loss of Y and closure of the four-membered ring to give I. This strategy proved successful (with Y = N_2) when Z = SO_2 (**1**),[1] but failed for Z = CR_2 (**2**),[2] Z = NR (**3**),[3] or Z = O (**4**).[4] Naphtho[1,8-*bc*]thiete (**5**), in which Z = S, seemed accessible using this approach if the proper precursor II were chosen.

Results and Discussion

Synthesis of Naphtho[1,8-*bc*]thiete (5). Naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide[7] (**7**, Scheme I) proved to be an excellent precursor of **5**. Ultraviolet irradiation of a dilute solution of **7** in benzene gave naphtho[1,8-*bc*]thiete (**5**) in up to 97% yield. This product could be obtained as white flakes melting at 40–42 °C. Proof of the structure of **5** is provided by its 300-MHz proton magnetic resonance and carbon-13 magnetic resonance spectra, which clearly show patterns consistent with a 1,8- (or 1,4- or 1,5-) symmetrically disubstituted naphthalene ring, and by its mass spectrum and osmometric molecular weight, which rule out a dimeric structure.

Oxidation of **5** with 1 equiv of *m*-chloroperbenzoic acid gave the corresponding sulfoxide (**6**, Scheme I), isolated as white crystals melting at 104–105 °C dec. The structure assignment is based on the infrared, nuclear magnetic resonance, and mass