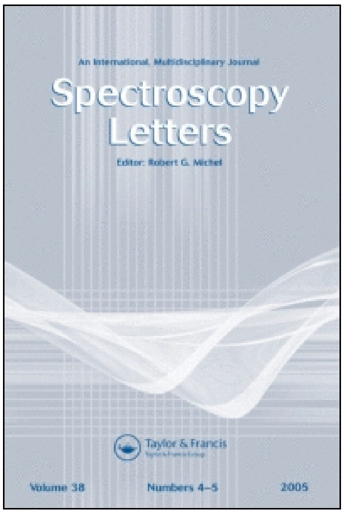

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Conformational Analysis of (S)-4,5,6,7-Tetrahydro-5-Methylimidazo [4,5,1-jk][1,4]-Benzodiazepin-2(1H)-one (R78362)

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To cite this Article Caldwell, Gary W. , Gauthier, A. Diane and Kukla, Michael J.(1993) 'Conformational Analysis of (S)-4,5,6,7-Tetrahydro-5-Methylimidazo [4,5,1-jk][1,4]-Benzodiazepin-2(1H)-one (R78362)', Spectroscopy Letters, 26: 6, 1005 — 1022

To link to this Article: DOI: 10.1080/00387019308011589

URL: http://dx.doi.org/10.1080/00387019308011589

SPECTROSCOPY LETTERS, 26(6), 1005-1022 (1993)

CONFORMATIONAL ANALYSIS OF (S)-4,5,6,7-TETRAHYDRO-5-METHYLIMIDAZO [4,5,1-jk][1,4]-BENZODIAZEPIN-2(1H)-ONE (R78362)

Key Works: TIBO Derivative, Benzodiazepine, ^{1}H NMR, X-ray Analysis, Conformational Analysis, Molecular Mechanics and MNDO-PM3 Calculations

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ABSTRACT

The solution and solid state conformation of (S)-4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-jk][1,4]-benzodiazepin-2(1H)-one (R78362) have been investigated by low temperature NMR and x-ray diffraction studies. The ^{1}H NMR spectrum of R78362 shows no evidence of the presence of multiple conformers in the temperature range 340K - 177K. Molecular mechanisms and semiempirical molecular orbital calculations suggest that the nitrogen and ring inversion barriers of R78362 are small and thus

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a time-averaged ^1H NMR spectrum is probably occurring at 298K. The x-ray diffraction data indicated that there were two independent molecules in the asymmetric unit of the crystal. The two molecules had similar conformations with the benzoimidazole ring being planar and the diazepine ring in a "half-chair" conformation.

INTRODUCTION

The tetrahydro-5-methylimidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-one and -thione (TIBO) derivatives were recently shown to inhibit *in vitro* the replication of HIV-1, but not HIV-2, by an effect on reverse transcriptase.[1,2] One of these TIBO compounds (R82913) had an IC50 of 1.5 nM for the growth inhibition of HIV/HIV-IIIb. The extraordinary potency and low cytotoxicity of R82913 gives it a selectivity index 3 times greater than that of 3′-azido-2′, 3′-dideoxythymidine (AZT). All TIBO derivatives have a common fused tricyclic ring system [Figure 1(R78362); a diazepine ring fused to a benzoimidazole ring] that vary structurally by substitution at the 6, 8, and/or 9 positions.[3,4] This prompted us to study the solution and solid state conformations of the diazepine-benzoimidazole base structure R78362. The synthesis [3] and the electron impact mass spectra [5] of R78362 have been reported.

EXPERIMENTAL

Variable-temperature ^1H NMR experiments were recorded on a Bruker AM-400 (400.13 MHz) Fourier transform spectrometer equipped with an Aspect 3000 data system. The samples were dissolved in methanol-d_4 (CD_3OD) or dimethylsulfoxide-d_6 (DMSO) at a concentration of ca. 20 mM. The chemical shifts were referenced to internal tetramethylsilane (TMS). Temperatures accurate to ±5K were measured externally using methanol as the standard. Typical ^1H NMR spectra were obtained using a pulse width of 3 μs (30°), a 1-s recycling

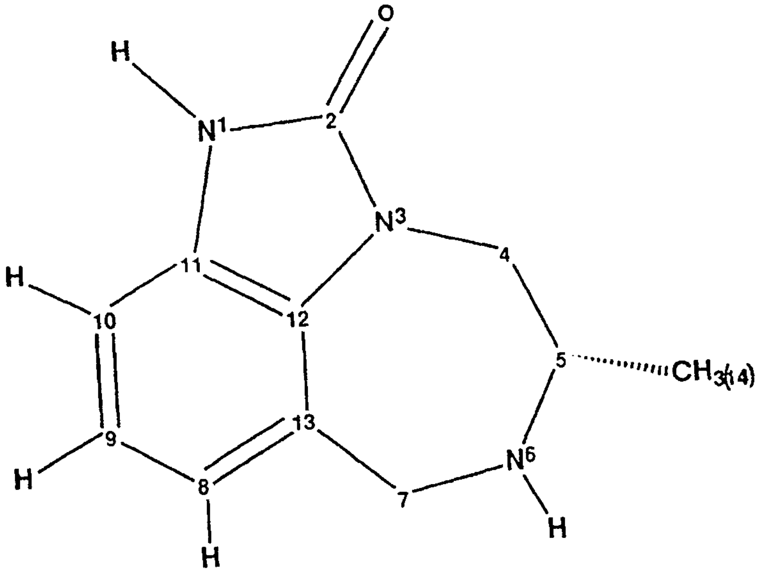


Figure 1: Structure and numbering scheme for R78362.

delay, 100 transients processed with a 0.1-Hz exponential weighting function and a spectral width of 8064 Hz over 32 768 data points, resulting in a digital resolution of 0.5 Hz per point.

The homonuclear correlated spectroscopy (COSY) and nuclear Overhauser enhancement (NOE) difference experiments were performed and processed using standard Bruker software. The COSY experiment utilized the following parameters: mixing pulse of 45°; 16 scans were measured for 128 values of t_1 to give a total data matrix of 128 x 1024 complex points with a spectral width of 2174 Hz. The FID was multiplied with a sine-bell function in both domains and symmetrized about the diagonal. The parameters for the NOE difference spectroscopy were as follows: irradiations were performed with 32 scans and two dummy scans at each frequency; a preirradiation delay of 2-3 s was used followed by a subsaturating irradiation period of similar duration. Prior to Fourier transformation, a 2 Hz line broadening function was applied to each FID.

The NMR spectral simulation program PANIC (Bruker software) was used to extract the coupling constants. Coupling constants are reported to ±0.5 Hz. The signs of the coupling constants have not been determined.

Single crystals of R78362 were grown from a slowly evaporated chloroform solution. Crystallographic data for R78362 were: $C_{11}H_{13}N_3O$, MW = 203.2 μ; monoclinic, space group $P2_1$-C_2^2; a=8.851(3)Å, b = 7.264(3)Å, c = 15.707(6)Å; $\alpha=\gamma=90°$, $\beta = 96.03(3)°$; V = 1004.3(6)$Å^3$; Z = 4; d_{calcd} = 1.344 g cm^{-3}; μ_a(CuKα) = 0.69 mm^{-1}. Data collection was performed on a computer-controlled Four-Circle Nicolet Autodiffractometer at 293±1K. A total of 1623 independent reflections were collected. The structure was solved using direct methods techniques. The resulting structural parameters were refined to convergence {R_1(unweighted, based on F) = 0.032} for 1569 independent reflections having 2Θ(CuKα)<120°} using counter-weighted full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for a nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The hydrogen atoms H1 and H6 for molecule I and II were located from a difference Fourier synthesis and refined as isotropic atoms. The methyl groups (C14 and its hydrogens) were refined as rigid rotors with sp^3-hybridized geometry and a C-H bond length of 0.96 Å. The refined positions for the rigid rotor methyl groups gave C-C-H angles which ranged from 104° to 114°. The remaining hydrogen atoms were fixed at idealized sp^2- or sp^3-hybridized positions with a C-H bond length of 0.96Å.

The molecular mechanics program SYBYL 5.5 (MAXIMIN2) and the semiempirical molecular orbital (MO) package MOPAC 5.0 with the

Table 1. Proton Chemical Shift Assignments of R78362 Relative to TMS.

CD$_3$OD (20 mM)			DMSO (20 mM)		
proton	δ (ppm)	$J_{H,H}$ (Hz)	proton	δ (ppm)	$J_{H,H}$ (Hz)
H1	a		H1	10.85	
H4	3.37	13.3 (4,4') 9.9 (4,5)	H4	3.15	
H4'	4.23	2.1 (4',5)	H4'	4.00-4.15	
H5	3.20	6.6 (5,14)	H5	3.08	6.5 (5,14)
H6	a		H6	2.65	
H7'	4.09-4.22	16.3 (7,7')	H7'	3.95	16.5 (7,7')
H7	4.09-4.22		H7	4.00-4.15	
H8	6.84		H8	6.65-6.90	
H9	6.92-7.00		H9	6.65-6.90	
H10	6.92-7.00		H10	6.65-6.90	
H14	1.31		H14	1.15	

a. H/D exchangeable proton

modified neglect of diatomic overlap-parametric method 3 (MNDO-PM3)[6] were used to study the conformational processes in R78362.

RESULTS AND DISCUSSION

Solution Conformational Analysis Using NMR

The structure and numbering scheme for R78362 are presented in Figure 1 and the ^{1}H chemical shifts and coupling constants are given in Table 1. The 400 MHz proton resonances were assigned by expected proton coupling relationships and ^{1}H -^{1}H COSY experiments with a couple of exceptions. The analysis of the proton resonances was initiated by the assignment of H14 methyl group. The H5 assignment was made based on the expected coupling to the methyl group which was also detected on the ^{1}H -^{1}H COSY map (not shown). The H4 resonance was located on the ^{1}H -^{1}H COSY map via its coupling to H5.

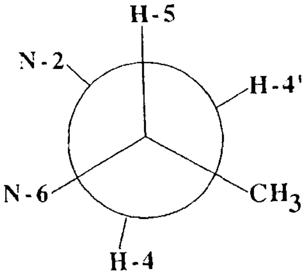


Figure 2: Newman project about the C5-C4 bond.

The H4′ resonance was located on the ^1H-^1H COSY map via its coupling to H4. THe H7 and H7′ protons were assigned to the AB spin-system between 4.09-4.22 ppm. The lack of any other significant proton coupling also supports this assignment. The aromatic H8 was differentiated from H9 and H10 by the NOE's observed from H8 to the H7 protons. When the H5 proton was irradiated strong NOE's were observed to the methyl group, the H4 and to both H7 protons.

The standard Karplus equation can be used to deduce approximate torsional angles about the C5-C4 bond.[7] For the vicinal coupling constant $J_{H,H}$ (4,5) = 9.9 Hz, a torsional angle of $ø = -168°$ is calculated for H5-C5-C4-H4. For $J_{H,H}$ (4′,5) = 2.1 Hz, a torsional angle of $ø = 68°$ is calculated for H5-C5-C4-H4′. A Newman projection for the C5-C4 bond is shown in Figure 2 to illustrate the above proton relationships.

The benzoimidazole ring is assumed planar with the seven-membered diazepine ring having greater mobility. Three conformational processes are considered for the seven-membered ring system : (1) nitrogen inversion about the N6 atom; (2) twists in the seven-membered ring defined by the torsional angle C7-C13-N3-C4; (3) ring inversion by torsion about the C13-C7-N6-C5 bonds. Nitrogen inversion and twisting

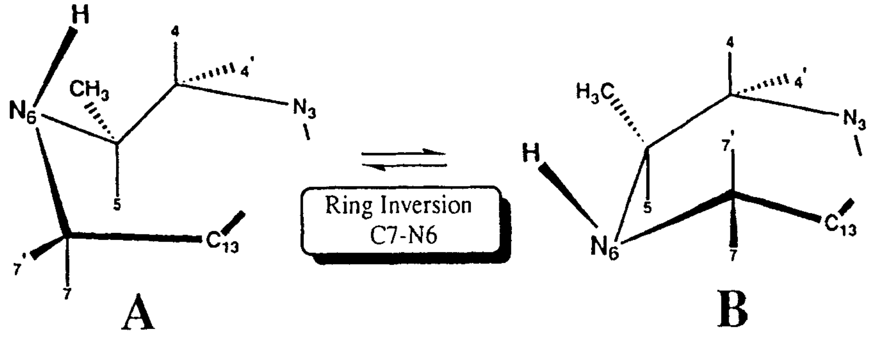


Figure 3: Ring inversion process for R78362

motions in flexible rings general have small energy barriers associated with them.[8] It is reasonable to expect that conformational processes (1) and (2) will have interconversion barriers less than the lower limit detectable in variable temperature NMR studies. Line shape analysis is restricted to conformational processes where $\Delta G^\ddagger$ is in excess of approximately 6 kcal/mol.[9] Thus the ring inversion is assumed to contribute to a greater extent than the other processes - the ring inversion is illustrated in Figure 3. It has been demonstrated that for (+)-(S)-4,5,6,7-tetrahydroimidazo-9-chloro-5-methyl-6-(3-methyl-2-butenyl) imidazo [4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione (TIBO; R82913) the **A** and **B** conformers are present.[10,11] It is interesting to note that both conformers will have a similar vicinal coupling constant between the H5 and H4 protons since the H5-C5-C4-H4 and H5-C5-C4-H4′ torsional angles are similar.[10,11] Thus a coupling constant analysis will not be useful to distinguish these conformers.

The conformation of the seven-membered diazepine ring can be further explored by variable temperature NMR experiments. A series of ^1H NMR spectra in DMSO over the temperature range 340K - 325K and in CD_3OD over the temperature range 325K - 177K reveal no significant

Table 2A. Atomic Coordinates for Nonhydrogen Atoms in Crystalline R78362 (Molecule I).[a]

Atom	Fractional Coordinates			Equivalent Isotropic Thermal Parameter
Type[b]	10^4x	10^4y	10^4z	B, Å^2 x 10 [c]
O	390(2)	2500(4)	6362(1)	54(1)
N3	1965(2)	2349(4)	5267(1)	37(1)
C2	1650(3)	2447(4)	6115(1)	41(1)
N1	3020(2)	2491(4)	6599(1)	41(1)
C11	4190(2)	2346(4)	6082(1)	35(1)
C12	3520(2)	2247(4)	5234(1)	33(1)
C4	740(2)	2022(4)	4598(1)	41(1)
C5	1053(2)	2659(4)	3710(1)	37(1)
N6	2259(2)	1608(3)	3367(1)	39(1)
C7	3812(3)	2211(4)	3630(1)	39(1)
C13	4417(2)	2145(4)	4559(1)	34(1)
C8	5983(3)	2078(4)	4794(2)	41(1)
C9	6629(3)	2186(4)	5619(2)	44(1)
C10	5736(3)	2338(4)	6293(2)	39(1)
C14	-430(3)	2459(6)	3116(2)	56(1)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. **b**. Atoms are labeled in agreement with Figure 4. **c**. This is one-third of the trace of the orthogonalized B_{ij} tensor.

signal broadening for the ^1H resonances of R78362. At temperatures above ca. 340K, R78362 in DMSO-d_6 decomposed. Since the ^1H NMR spectrum of R78362 shows no evidence for the presence of multiple conformers, we can conclude that either one form is present in large excess or that two or more forms are in fast exchange on the chemical-shift time scale. The first explanation of a single conformer seems unlikely since many compounds that contain a seven-membered ring with two torsional constraints are flexible. [8] We conclude that the rates for all conformational processes are fast (low barriers to interconversion) and a time-averaged ^1H NMR spectrum results at room temperature.

Table 2B. Atomic Coordinates for Nonhydrogen Atoms in Crystalline R78362 (Molecule II).[a]

Atom	Fractional Coordinates			Equivalent Isotropic Thermal Parameter
Type[b]	10^4x	10^4y	10^4z	B, Å^2 x 10[c]
O	3674(2)	-800(3)	1434(1)	45(1)
N3	3033(2)	1195(3)	291(1)	33(1)
C2	3109(2)	621(4)	1135(1)	34(1)
N1	2427(2)	1974(3)	1566(1)	38(1)
C11	2024(2)	3432(4)	1027(1)	34(1)
C12	2397(2)	2943(3)	209(1)	31(1)
C4	3863(3)	187(4)	-318(1)	35(1)
C5	3207(3)	407(4)	-1252(1)	35(1)
N6	3376(2)	2257(3)	-1588(1)	36(1)
C7	2212(3)	3578(4)	-1404(1)	38(1)
C13	2078(2)	4112(4)	-489(1)	33(1)
C8	1468(3)	5808(4)	-316(2)	41(1)
C9	1144(3)	6320(4)	508(2)	45(1)
C10	1405(3)	5134(4)	1189(2)	42(1)
C14	4027(3)	-954(5)	-1779(2)	47(1)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. b. Atoms are labeled in agreement with Figure 4. c. This is one-third of the trace of the orthogonalized B_{ij} tensor.

Solid State Conformational Analysis Using X-ray Diffraction

The solid state structure of R78362 was determined by an x-ray diffraction investigation of a single crystal. The final positional parameters of the nonhydrogen atoms are in Table 2 (A and B) and their thermal parameters in Table 3. Positional parameters of the H atoms are in Table 4. Bond distances and angles are in Tables 5 and 6 respectively. Hydrogen-bond distances and angles are in Table 7.

X-ray diffraction analysis reveal that there are two independent molecules (denoted as molecules I and II) in the asymmetric unit of the crystal, which are hydrogen-bonded through the seven-membered diazepine N6 atom and the hydrogen atom of the N1 atom of the

Table 3. Anisotropic Thermal Parameters for Nonhydrogen Atoms in Crystalline R78362 (Molecules I and II).[a,b]

Atom	Anisotropic Thermal Parameters (Å^2 x 10)					
Type[c]	B11	B22	B33	BI2	BI3	B23
			Molecule I			
O	37(1)	94(1)	33(1)	-1(1)	10(1)	-4(1)
N3	35(1)	53(1)	22(1)	-1(1)	5(1)	-1(1)
C2	41(1)	58(1)	24(1)	-2(1)	5(1)	-1(1)
N1	40(1)	63(1)	21(1)	-1(1)	3(1)	0(1)
C11	41(1)	39(1)	24(1)	-0(1)	3(1)	2(1)
C12	35(1)	36(1)	28(1)	-1(1)	4(1)	1(1)
C4	36(1)	58(1)	27(1)	-6(1)	2(1)	-2(1)
C5	40(1)	45(1)	25(1)	1(1)	-1(1)	-0(1)
N6	50(1)	43(1)	24(1)	1(1)	4(1)	-2(1)
C7	44(1)	47(1)	28(1)	2(1)	10(1)	3(1)
C13	39(1)	35(1)	30(1)	1(1)	8(1)	1(1)
C8	39(1)	46(1)	40(1)	1(1)	11(1)	2(1)
C9	36(1)	46(1)	49(1)	1(1)	2(1)	3(1)
C10	38(1)	42(1)	36(1)	-2(1)	-3(1)	3(1)
C14	49(1)	84(2)	33(1)	-4(1)	-4(1)	3(1)
			Molecule 2			
O	51(1)	50(1)	34(1)	11(1)	4(1)	10(1)
N3	37(1)	37(1)	25(1)	5(1)	4(1)	2(1)
C2	34(1)	42(1)	26(1)	4(1)	1(1)	3(1)
N1	43(1)	48(1)	24(1)	5(1)	5(1)	-0(1)
C11	31(1)	42(1)	29(1)	2(1)	4(1)	-4(1)
C12	27(1)	36(1)	28(1)	-0(1)	3(1)	-1(1)
C4	40(1)	39(1)	27(1)	6(1)	3(1)	-1(1)
C5	33(1)	45(1)	27(1)	-2(1)	3(1)	-4(1)
N6	35(1)	49(1)	24(1)	-6(1)	5(1)	1(1)
C7	43(1)	44(1)	28(1)	0(1)	1(1)	8(1)
C13	29(1)	38(1)	31(1)	-2(1)	2(1)	3(1)
C8	39(1)	41(1)	42(1)	5(1)	1(1)	6(1)
C9	40(1)	39(1)	55(1)	9(1)	5(1)	-5(1)
C10	40(1)	50(1)	37(1)	6(1)	6(1)	-10(1)
C14	51(1)	56(1)	34(1)	10(1)	6(1)	-9(1)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. **b**. The form of the anisotropic thermal parameter is given in reference 12. **c**. Atoms are labeled in agreement with Figure 4.

Table 4. Atomic Coordinates for Hydrogen Atoms in Crystalline R78362.[a]

Atom	Fractional Coordinates		
Type[b]	10^4x	10^4y	10^4z
		Molecule I	
H1	3181(24)	2464(43)	7128(15)
H4A	542	722	4572
H4B	-146	2657	4748
H5	1396	3913	3748
H6	2108(28)	328(45)	3533(17)
H7A	4470	1459	3327
H7B	3883	3468	3449
H8	6641	1952	4349
H9	7715	2155	5737
H10	6177	2435	6876
H14A	-294	2905	2554
H14B	-1132	3241	3371
H14C	-823	1227	3076
		Molecule II	
H1	2292(50)	1948(79)	2283(25)
H4A	4893	622	-263
H4B	3850	-1097	-175
H5	2134	178	-1286
H6	4410(27)	2682(45)	-1448(15)
H7A	2399	4688	-1708
H7B	1250	3070	-1628
H8	1259	6670	-777
H9	733	7519	597
H10	1170	5469	1752
H14A	3985	-2189	-1565
H14B	5066	-555	-1743
H14C	3593	-921	-2365

a. The isotropic thermal parameters for H1 and H6 were refined to final values of 3.8(5)Å^2 and 4.7(6)Å^2 for molecule I and 13(1)Å^2 and 4.3(5)Å^2 for molecule I I. The remaining hydrogen atoms were fixed at 1.2 times the equivalent isotropic thermal parameter of the carbon atom to which it is covalently bonded. b. Hydrogen atoms are labeled with the same subscript(s) as the nitrogen or carbon atoms to which they are covalently bonded with an additional literal subscript (A, B or C) where necessary to distinguish between hydrogens bonded to the same carbon atom.

Table 5. **Bond Length Involving Nonhydrogen Atoms in Crystalline R78362.**[a]

Type[b]	Length, Å	Type[b]	Length, Å
Molecule I		Molecule II	
O-C2	1.219(3)	O-C2	1.220(3)
N3-C2	1.392(3)	N3-C2	1.385(3)
N3-C12	1.384(3)	N3-C12	1.389(3)
N1-C2	1.362(3)	N1-C2	1.369(3)
N1-C11	1.386(3)	N1-C11	1.379(3)
N3-C4	1.448(3)	N3-C4	1.462(3)
N6-C5	1.461(3)	N6-C5	1.457(4)
N6-C7	1.461(3)	N6-C7	1.459(3)
C11-C12	1.402(3)	C11-C12	1.406(3)
C11-C10	1.373(3)	C11-C10	1.386(4)
Cl2-C13	1.391(3)	Cl2-C13	1.392(3)
C13-C8	1.397(3)	C13-C8	1.383(4)
C8-C9	1.363(3)	C8-C9	1.405(4)
C9-C10	1.390(4)	C9-C10	1.375(4)
C4-C5	1.523(3)	C4-C5	1.529(3)
C5-C14	1.535(3)	C5-C14	1.522(4)
C7-C13	1.502(3)	C7-C13	1.506(3)
N1-H1	0.83(2)	N1-H1	1.14(4)
N6-H6	0.98(3)	N6-H6	0.97(2)

a.The numbers in parentheses are the estimated standard deviations in the last significant digit. b. Atoms are labeled in agreement with Figure 4.

benzoimidazole ring (Figure 4). Packing of the molecules in the unit cell is determined largely by hydrogen bonding. The benzoimidazole and the diazepine rings stack over each other with the hydrogen atom of the N6 atom hydrogen-bonded to the oxygen atom on a benzoimidazole ring. The two independent molecules have similar conformations. The

Table 6. Bond Angles Involving Nonhydrogen Atoms in Crystalline R78362.[a]

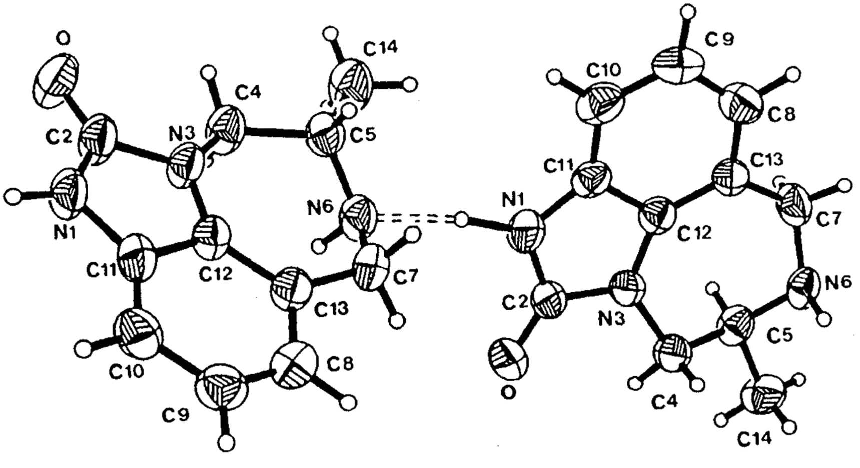
Type[b]	Angle, (deg)	Type[b]	Angle, (deg)
Molecule I		Molecule II	
C2N3Cl2	109.8(2)	C2N3Cl2	110.0(2)
C2N3C4	119.5(2)	C2N3C4	119.9(2)
C12N3C4	129.5(2)	C12N3C4	128 6(2)
C2N1C11	110.4(2)	C2N1C11	110.3(2)
C5N6C7	116.2(2)	C5N6C7	115.7(2)
OC2N3	126.1(2)	OC2N3	127.0(2)
OC2N1	127.7(2)	OC2N1	126.9(2)
N3C2N1	106.2(2)	N3C2N1	106.1(2)
N1C11C12	107.0(2)	N1C11C12	107.3(2)
N1C11C10	130.2(2)	N1C11C10	130.8(2)
C12C11C10	122.7(2)	C12C11C10	121.9(2)
N3C12C11	106.6(2)	N3C12C11	106.2(2)
N3C12C13	132.9(2)	N3C12C13	132.6(2)
C11C12C13	120.5(2)	C11C12C13	121.2(2)
C12C13C7	124.4(2)	C12C13C7	124.4(2)
C12C13C8	115.5(2)	C12C13C8	116.1(2)
C7C13C8	120.0(2)	C7C13C8	119.2(2)
C13C8C9	123.7(2)	C13C8C9	122.5(2)
C8C9C10	120.9(2)	C8C9C10	121.2(3)
C11C10C9	116.6(2)	C11C10C9	117.0(2)
N3C4C5	114.8(2)	N3C4C5	114.1(2)
C4C5N6	112.9(2)	C4C5N6	113.6(2)
C4C5C14	107.5(2)	C4C5C14	107.4(2)
N6C5C14	109.8(2)	N6C5C14	109.2(2)
N6C7C13	119.6(2)	N6C7C13	119.1(2)
C2N1H1	128(2)	C2N1H1	125(3)
C11N1H1	122(2)	C11N1H1	125(3)
C5N6H6	106(2)	C5N6H6	110(2)
C7N6H6	111(1)	C7N6H6	115(2)

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. **b.** Atoms are labeled in agreement with Figure 4.

Table 7. **Close Contacts Involving Hydrogen Atoms in Crystalline R78362.** [a]

Donor Atom (D)[b]	Acceptor Atom (A)	Distance A D...A	Distance A H...A	Angle deg. D-H...A	Angle deg. H-D...A	Angle deg. H...A-X[c]
N1[I]-H1[I]	N6[II]	2.838(3)	2.01(2)	174(2)	4(2)	116(2) C5[II] 99(2) C7[II] 101(4) H6[II]
N1[II]-H1[II]	N1[I]	2.860(3)	1.72(4)	171(3)	5(3)	112(3) C5[I] 97(3) C7[I] 115(5) H6[I]
N6[II]-H6[II]	O[II]	2.955(3)	2.02(2)	161(2)	13(2)	6(2) C2[II]

a. The numbers in parentheses are the estimated standard deviations in the last significant digit. The letter in the square bracket denotes molecule I and molecule II. **b**. The hydrogen atom involved in the interaction is also indicated. **c**. The symbol X is used to denote an atom which is covalently bonded to the acceptor nitrogen or oxygen atom.



Molecule II

Molecule I

Figure 4: ORTEP diagram of R78362

benzoimidazole ring is planar with the diazepine ring in the **A** conformation (Figure 3 and Tables 5 and 6).

The x-ray data indicated that the torsional angle of H5-C5-C4-H4 was ø = -175° while the torsional angle of H5-C5-C4-H4′ was ø =66.9°. These results are comparable to those deduced from solution phase data utilizing the standard Karplus equation. Thus the torsional angles about the C5-C4 bond appears to be similar in solution and the solid state (Figure 2).

It is of interest to compare the x-ray structure of R78362 with that of R82913 determined in an earlier study.[10] In both molecules the benzoimidazole ring is planer. R78362 has its seven-membered diazepine ring in the **A** conformation while R82913 is in two distinct **A** and **B** conformations (Figure 3). The **A** conformation of R78362 and R82913 can be compared by examining the torsion angles along two bonds of the diazepine ring: C5-N6 (-84.2 in R78362 and -83.4 in R82913) and N6-C7 (62.6 in R78362 and 68.8 in R82913). The conformations of the diazepine rings are surprisingly similar even though R78362 is a secondary amine while R82913 is a tertiary amine.

Theoretical Conformational Analysis

The molecular mechanisms calculations indicated that the difference in energy between ground states for the nitrogen inversion species was 1.1 kcal/mol with the **A** conformation (the N6 lone-pair electrons point away from the center of the molecule) having the lower energy and 0.3 kcal/mol with the **B** conformation (the N6 lone-pair electrons point away from the center of the molecule) having the lower energy. The **A** conformation bond lengths, bond angles and torsional angles calculated by molecular mechanisms and MNDO-PM3 are in excellent agreement with those measured by our x-ray study. The nitrogen inversion barrier, which was obtained by assuming a planar nitrogen transition state specie minus that of the ground state, was 3.8

kcal/mol for **A** and 3.6 kcal/mol for **B**. These results lead us to conclude that the rate for nitrogen inversion is fast (low barriers to interconversion) and probably not detectable in variable temperature NMR studies.

The difference in energy between ground states for the ring inversion species **A** and **B** was 0.7 kcal/mol with the **A** conformer having the lower energy. The transition state was determined using the SADDLE program in the MOPAC package. [6] The ring inversion barrier, which was obtained by assuming the above ring transition state specie minus that of the ground state, was 10.0 kcal/mol. These results lead us to conclude that the rate for ring inversion is probably detectable in variable temperature NMR studies at temperatures below 177 K.

The twists inversion barrier in the seven-membered ring defined by the torsional angle C7-C13-N3-C4 was not determined. These pseudorotations typically have low barriers associated with them [8] and thus are not detectable in variable temperature NMR studies.

Conclusion

The solution and solid state conformation of (S)-4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-jk][1,4]-benzodiazepin-2(1H)-one (R78362) have been investigated. The benzoimidazole ring is assumed planar with presumably the seven-membered diazepine ring having different conformations. The low temperature ^1H NMR spectrum of R78362 shows no evidence of the presence of multiple conformers in the temperature range 340K - 177K. Molecular mechanisms and semiempirical molecular orbital calculations suggest that the nitrogen and ring inversion barriers of the seven-membered diazepine ring are small and thus suggests that a time-averaged ^1H NMR spectrum is probably occurring between 340K - 177K. The x-ray diffraction data indicated that there were two independent molecules in the asymmetric unit of the crystal. The two molecules had similar conformations with the benzoimidazole ring being planar and the diazepine ring in a "half-chair" conformation. The torsional angles about the C5-C4 bond appears to be similar in solution and the solid state.

ACKNOWLEDGMENTS

We appreciate the assistance of H.J. Breslin for obtaining all compounds and Dr. Cynthia Day of Crystalytics Co. for the crystallographic analysis of R78362.

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Date Received: January 7, 1993

Date Accepted: February 15, 1993