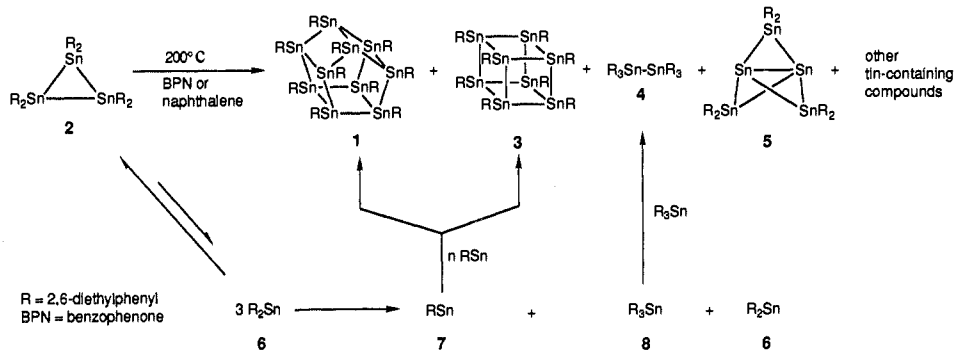
Scheme I



for aryl group rotation in **3** is <-80 °C. As revealed by ^{119}Sn NMR spectroscopy, the single resonance observed for **1**[9] is 66 ppm upfield from that of **3**, and this is opposite to the downfield ^{13}C chemical shift of $[HC]_{10}$ relative to $[HC]_8$.[11] In addition, the expected $^3J(^{119}Sn-^{117}Sn)$ coupling satellites[12] are not observed for either **1** or **3**, and on the basis of the Karplus correlation between dihedral angle and vicinal coupling constants, it is assumed that the magnitudes of these tin-tin coupling constants are near 0 due to the 90° dihedral angle in both molecular frameworks.[13] Finally, the electronic spectra of **1** and **3** in hexane are remarkably different from each other, with no well-defined maxima being observed for the former.[9,10]

Concerning the relative stabilities of the two perstanna[*n*]prismanes, heating of solutions of pure **1** or **3** in toluene at 200 °C shows no interconversion between the two species, and while both compounds are relatively stable at this temperature, **3** was observed to decompose to a greater extent than **1**, which remains unchanged, as determined by ^1H NMR spectroscopy. This increased stability of **1** over **3** is in keeping with the prediction that $[HSn]_{10}$ should be more stable than $[HSn]_8$.[14] Finally, a solution of **1** in methylcyclohexane remained unchanged upon photolysis at room temperature using a Hanovia high-pressure lamp.

Crystallographic Analysis.[10] As shown in Figure 1, the tin-tin-bonded molecular framework of **1** is composed of two five-membered rings which are held together by five inter-ring bonds. The mean tin-tin bond length of 2.856 (2) Å within the five-membered rings is identical with the value found for the mean inter-ring tin-tin bond length, and this value can be compared with the mean tin-tin bond length in **3**, which is 2.854 (2) Å. The average bond angles within the five-membered and four-membered rings of **1** are 108.0 (1)° and 90.0 (1)°, respectively, and both of these are exactly the values of the geometric ideals. For Sn-Sn-C bond angles in **3**, the average value is 125.1 (4)°, and in **1**, the average value for this angle for tin atoms on adjacent five-membered rings is 124.1 (4)° while it is 119.0 (4)° for tin atoms within the same five-membered ring. Surprisingly, all three of these mean bond angles are in very close agreement with those calculated for $[HM]_8$ and $[HM]_{10}$ (M = C, Si), even in spite of the steric interactions between adjacent 2,6-diethylphenyl ligands in the perstanna[*n*]prismanes.[1h,15]

In conclusion, perstanna[*n*]prismanes, $[RSn]_{2n}$, where $n = 4$ and 5, have been shown to be isolable compounds when the steric demands of the organic ligand are sufficient to kinetically stabilize these structures. In the present study, the 2,6-diethylphenyl ligand appears to be the ideal choice for stabilization of **1** and **2**; however, by carefully modelling the steric requirements, other perstanna-[*n*]prismanes, where $n = 2$, 3, or 6, should be accessible from the appropriate stannylene precursors.

Acknowledgment. We thank Dr. Cynthia Day of Crystalytics Co. for the crystallographic analysis of **1** and the National Science Foundation (Grant CHE-9001462) for support of this work. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supplementary Material Available: Detailed information concerning the spectroscopic and crystallographic analysis of **1**, including listings of atomic coordinates and temperature factors, bond lengths, bond angles, and anisotropic temperature factors (30 pages). Ordering information is given on any current masthead page.

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Molecular Structure of a Potent HIV-1 Inhibitor Belonging to the TIBO Family

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A series of tricyclic tetrahydroimidazo[4,5,1-*jk*]benzodiazepin-2(1*H*)-one (TIBO) and -thione derivatives have been found to be highly effective inhibitors of the reverse transcriptase (RTase) of HIV-1, the principal etiological agent of AIDS.[1] One of the derivatives, coded R82913 ($C_{16}H_{20}N_3SCl$; Figure 1), has an IC_{50} of 1.5 nM for the growth inhibition of HIV-1/HIV-IIIb. The extraordinary potency of this compound, together with its relatively low cytotoxicity, gives it a selectivity index 3 times greater than that of AZT (3′-azido-2′,3′-dideoxythymidine), at present the only drug approved for the treatment of AIDS.[2] It would be of great interest to investigate the structure of these compounds to gain insight on their unusual specificity toward RTase. The crystal structures of a number of nucleoside derivatives with anti-AIDS activity have been determined. These

* Corresponding author.

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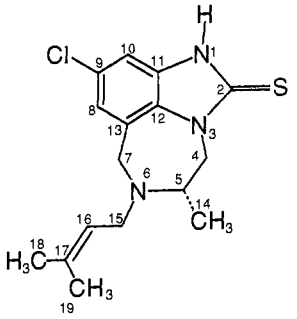

TIBO

Figure 1. Molecular representation of (+)-(*S*)-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione with the numbering system.

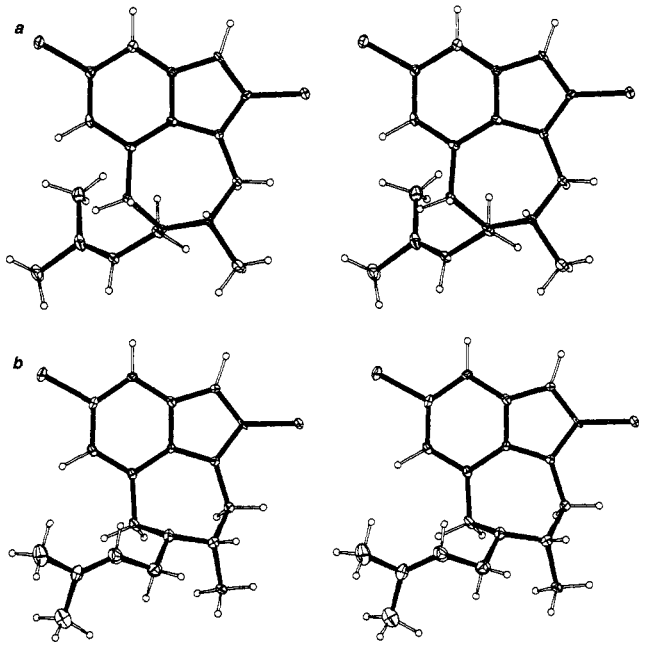

Figure 2. Stereoscopic ORTEP diagrams of molecules A (a) and B (b).

include AZT,[3a-d] 3′-azido-2′,3′-dideoxyuridine,[3d] 3′-azido-2′,3′-dideoxy-5-ethyluridine,[3d] 2′,3′-dideoxycytidine,[4] 2′,3′-dideoxyadenosine,[5] 3′-deoxythymidine,[6] 3′-fluoro-3′-deoxythymidine,[7] 2′-fluoro-2′,3′-dideoxyarabinosyladenine,[8] and 2′-fluoro-2′,3′-dideoxyarabinosylhypoxanthine.[8]

X-ray diffraction analysis of R82913 reveals that there are two independent molecules (designated A and B) in the asymmetric unit of the crystal, having rather different conformations (Figure 2, parts a and b).[9,13] They mutually interact by forming reciprocal

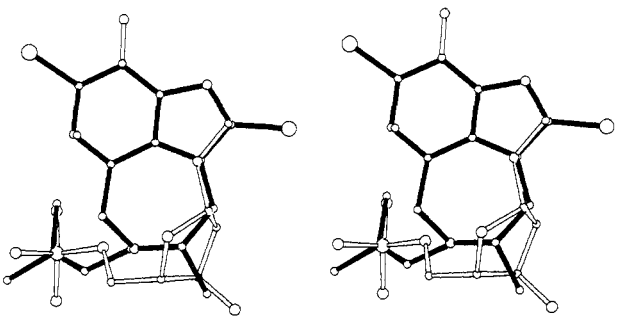

Figure 3. A superposition of R82913 (conformer A; filled bonds) to deoxyadenosine 5′-monosphosphate (open bonds; ref 21) with adenine in the syn conformation.

hydrogen bonds between N1 and S ($N1_A$–S_B, 3.249 (6) Å; $N1_B$–S_A, 3.310 (6) Å). The benzoimidazole rings stack over each other, with the thione group lying over the fused tricyclic ring system near its center (location close to C12) on one side and the chlorine atom lying under the imidazole ring on the other side. The methylbutenyl groups from molecules A and B are packed together in the lattice using only van der Waals forces (Figure 1S, supplementary material), resulting in large temperature factors for those side chains.

In both molecules the benzoimidazole ring (including N1, C2, N3, C8–C13, Cl, and S atoms) is mostly planar. Molecule A has its seven-membered diazepine ring in the *TS* conformation.[14] The methylbutenyl group is above the mean plane, with C15 at the axial position and the H16 pointing away from the molecule. In contrast, the diazepine ring of molecule B is in the *TC/BS* conformation[14] with C15 in an equatorial position. The conformational changes can be described mainly by the torsion angles along two bonds of the seven-membered ring: C5–N6 (−83.4° in A and 46.2° in B) and N6–C7 (68.8° in A and −93.8° in B). The torsion angle along the C15–C16 bond remains similar in the two mol-

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(9) Crystals of R82913 with an elongated rod shape were grown from a mixture of a methanol–water 10 mM solution by slow evaporation at room temperature.[10] Two independent datasets were collected, one (crystal size 0.2 × 0.2 × 0.4 mm) on a Rigaku AFC-5R rotating anode X-ray diffractometer at 25 °C using the ω-scan mode with Cu Kα radiation (to $2\theta = 120°$; 0.89-Å resolution) and the other (crystal size 0.2 × 0.2 × 0.6 mm) on an Enraf-Nonius CAD4 diffractometer at −110 °C using variable scan with Mo Kα radiation (to $2\theta = 60°$; 0.71-Å resolution). After Lp and absorption correction, there were 2476 (out of 2656) and 3198 (out of 4952) independent reflections observed at the 4.0 $\sigma(F)$ level above the background, and they were used in the refinement. Their crystal structures are designated as RT and LT structures, respectively. The LT dataset has 81% observed reflections to 0.9-Å resolution and 48% between 0.9- and 0.71-Å resolution. They were in the monoclinic space group $C2$ with a = 31.384 (6) Å, b = 10.747 (2) Å, c = 9.975 (2) Å, and β = 92.19 (2)° for RT and a = 30.938 (6) Å, b = 10.653 (3) Å, c = 9.880 (5) Å, and β = 93.22 (3)° for LT. The RT structure was solved first by direct methods using the program SHELXS-86.[11] It was refined by full-matrix least squares using the NRCVAX package.[12] There are two independent R82913 molecules in the asymmetric unit. All 42 non-hydrogen atoms were refined anisotropically. Forty hydrogen atoms were also included in the refinement with fixed positions and isotropic temperature factors. The final R factors are 4.8% (RT) and 5.4% (LT), which are slightly higher than that from an exceptionally well refined structure. This may be due to the less ordered methylbutenyl side chains in the molecules discussed in the text. The LT structure was refined with better temperature factors, and their atomic coordinates (listed in Table 1S, supplementary material) are used for discussions in this paper.

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(14) The diazepine conformation is defined as described by Boessenkool and Boeyens (Boessenkool, I. K.; Boeyens, J. A. *J. Cryst. Mol. Struct.* **1980**, *10*, 11–18). Molecule A has the puckering amplitudes of q_2 = 0.15 Å and q_3 = 0.53 Å and pseudorotation ϕ_2 = 150.7° and ϕ_3 = 165.8°. Molecule B has q_2 = 0.80 Å and q_3 = 0.36 Å and ϕ_2 = 29.0° and ϕ_3 = 145.2°.

ecules (124.9° in A and 123.9° in B) despite the different dispositions of the methylbutenyl group. The conformation of this type of diazepine ring (fused to a benzo ring) that is seen in molecule B occurred more frequently (in 111 out of 122 molecular fragments) according to our search of the current Cambridge Data Base.

The differences in the conformation have some effects on the geometry associated with the diazepine ring and the methylbutenyl side chain. The most prominent features are the bond angles at the N3 and C13 atoms. The endocyclic angles of C4-N3-C12 and C7-C13-C12 in A (127.6 (5)° and 123.9 (6)°) are significantly greater than those of B (124.1 (5)° and 119.5 (6)°). In addition, some bond lengths associated with the C5 and N6 atoms and the methylbutenyl group for A/B molecules have variations greater than 5 esd's. The differences associated with the methylbutenyl group are likely due to their large temperature factors described earlier. Other differences may be related to the conformation around nitrogen N6. Both N6 atoms have sp^3 character as reflected in the distance of N6 from the plane of C5, C7, and C15 (0.360 (6) Å for A and 0.368 (7) Å for B). Notice that N6 retains the same chirality (*S*) in both conformers and its lone-pair electrons point away from the center in molecule A, but toward the center in molecule B.

The observation of two distinct conformations in the crystal suggests that at least two conformers are in equilibrium in solution. A series of one-dimensional NMR spectra at different temperatures showed that two molecular species coexist in equilibrium on the NMR time scale up to 20 °C.[15] At -40 °C, these two species are clearly resolved into two populations (90%:10%). Interconversion of the two conformers involves flipping of the methylbutenyl side chain from one side of the aromatic ring plane to the other side, with modest energy barriers. The difference in total energies associated with these two conformers is 1.3 kcal/mol on the basis of the calculation using MOPAC[17] with PM3 force field parameters.[18] Conformation A has lower energy, and this suggests that it is the major species in solution. These two conformers may be considered as atropisomers, reminiscent of an ansamycin antibiotic, streptovaricin C,[19] also an inhibitor for RTase.

The mode of action of R82913 appears to be quite different from that of the dideoxynucleosides.[2,20] Whether the conformations seen in the present crystal structure or the flexibility associated with the diazepine ring is relevant to its biological function as an inhibitor for the RTase of HIV-1 remains to be conclusively answered by solving the structure of the complex between RTase and the inhibitor. However, it is interesting to note that the molecule contains a conjugated ring system not unlike a purine ring. A superposition of molecule A with deoxyadenosine 5′-monophosphate[21] (with adenine in the syn conformation) reveals the overall similarity between them (Figure 3). It is conceivable that the nucleotide triphosphate binding site in RTase has a cavity that can accommodate this inhibitor and bind it extremely tightly. It has been previously noted that nucleoside analogues containing an ethylene moiety such as a cyclopentene ring are excellent inhibitors for enzymes in the nucleoside synthesis pathway[22] and for HIV viruses.[2]

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Supplementary Material Available: A table of the fractional atomic coordinates of the two independent molecules of R82913 of the LT form and a figure showing the packing interactions (3 pages). Ordering information is given on any current masthead page.

(15) NMR spectra were recorded on a GE GN-500 500-MHz spectrometer. The sample was 20 mM R82913 in deuterated methanol. The temperature range was from -60 °C to 40 °C. The smaller population (10%) starts to become evident at 0 °C for some resonances. The population ratio remains unchanged throughout the temperature range. However, the crystallization process selects out the 1:1 ratio of the two conformers to form the crystal lattice, thereby shifting the equilibrium in solution. This phenomenon is quite common in the crystallization of many biological macromolecules. For example, the minor species Z-DNA, instead of the abundant B-DNA, crystallized from the low-salt solution of d(CGCGCG) readily.[16]

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Iron Chelate Mediated Proteolysis: Protein Structure Dependence

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Cleavage of DNA or RNA by metal chelates is an important new approach to characterizing important structural features of nucleic acids and their complexes in solution.[1] Naturally occurring proteases and selective peptide cleaving agents are useful for dissecting protein structure and function, but more choices are desirable.[2] Artificial proteolytic reagents which are directed by *proximity* rather than by residue type represent a new approach which could be employed for sequence analysis, functional analysis of structural domains, or determining the spatial arrangement of subunits within a supramolecular structure. They could also be incorporated into new, targeted therapeutic agents.

Recently, there has been considerable interest in the cleavage of proteins by metal ions or chelates bound at particular sites.[3,4] In our laboratories, site-specific cleavage of proteins is achieved by introducing a metal-binding site at one position in a polypeptide chain. Recently, we found that an iron chelate attached to cysteine-34 of the protein bovine serum albumin hydrolyzed the protein backbone at two sites—between Ala-150 and Pro-151, and between Ser-190 and Ser-191—without excessive decomposition of amino acid side chains.[4a]

This approach could permit mapping a site of interest by determining which individual peptide bonds are adjacent to it. However, because no crystal structure is available for bovine serum albumin, no detailed information concerning the steric require-

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