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Chirality in Unsymmetrically Substituted Benzopentathiepins: The Result of a High Barrier to Ring Inversion

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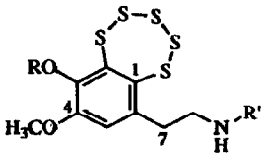
Abstract: The ^{1}H NMR spectrum of varacin (1), the first naturally-occurring compound determined to bear a 1,2,3,4,5-benzopentathiepin ring, shows unexpectedly complex signals for the side chain methylene protons. Evidence is presented which indicates that unsymmetrically substituted benzopentathiepins are asymmetric molecules as a result of a high energy barrier to inversion of the low energy chair conformations of the polysulfide ring. Derivatization of varacin with a chiral auxiliary provides diastereomeric products which can be separated by fractional recrystallization.

Organic polysulfides have received considerable attention in the past few years, both for their unique chemical structures and for their often significant biological activities.[1] Varacin (**1**),[2] the first naturally-occurring benzopentathiepin, was isolated from a marine ascidian, and its unique dopamine-derived structure was recently confirmed by two separate syntheses.[3,4] In our synthetic communication,[3] we reported that the NMR signals assigned to the side chain methylene protons were unexpectedly complex, attributing this to restricted rotation of the side chain. We would now like to present evidence indicating that the signal complexity is the result of a high barrier to inversion of the pentathiepin ring, which induces asymmetry into the molecule, causing the protons to become diastereotopic.



1 R = CH_3; R' = H
2 R = CH_3; R' = $CO_2CH_2CH_2Si(CH_3)_3$
3 R = $CH_2OCH_2CH_2Si(CH_3)_3$; R' = $CO_2CH_2CH_2Si(CH_3)_3$
4 R = $CHCH_3OCH_2CH_3$; R' = $CO_2CH_2CH_2Si(CH_3)_3$

In an effort to understand the role of side chain mobility on the multiplicity of the H7 NMR signals, variable temperature NMR experiments were performed on β-(trimethylsilyl)-ethoxycarbonyl (TEOC) protected varacin (**2**). An increase in temperature from 25 to 100 °C caused the signals to sharpen, supporting increased mobility, but instead of coalescing, distinctly diastereotopic signals for methylene protons H7 were observed. These results are explained only by the presence of asymmetry in the molecule, indicating that, at least on the NMR time scale, unsymmetrically substituted benzopentathiepins, such as varacin, are chiral.

Further support for this hypothesis is observed in the ^{1}H NMR spectrum of varacin analog **3** (Figure 1A), which was prepared as part of an effort to synthesize lissoclinotoxin A.[5,6,7] The methylene protons attached to both oxygen-bearing carbons of the SEM protecting group are diastereotopic. The protons on the doubly oxygenated carbon (**a**) comprise an AB system, while those on the singly oxygenated carbon (**b**) are

each present as an apparent quartet. Furthermore, when a chiral center is incorporated into the phenol protecting group, as in compound **4**, diastereomers are formed, resulting in a doubling of the signals assigned to both the secondary methyl group (**a**) and the methylene (**b**) of the ethoxyethyl moiety (Figure 1B). Because the doubling of signals is observed only in the presence of the pentathiepin ring, and not for the trithiole analog or the TEOC-protected *bis*-sulfide precursor,[3] the possibility that it is simply the result of cis/trans isomerization of the carbamate moiety can be ruled out.

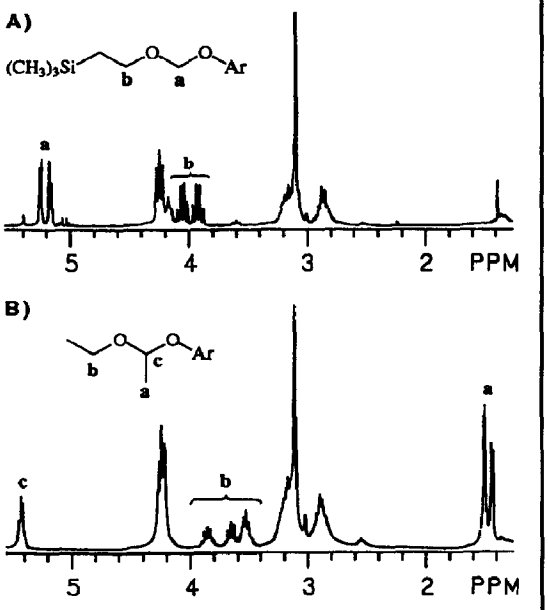
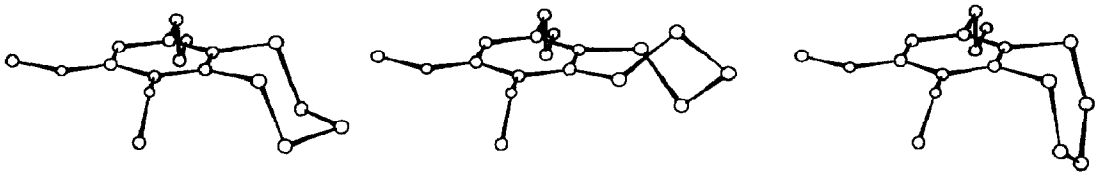


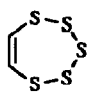
Figure 1. Partial ^1H NMR spectra of (A) compound **3** and (B) compound **4** Both spectra were recorded in C_6D_6 at 300 MHz.

Molecular mechanics calculations[8,9] performed on varacin suggest that a chair conformation, as depicted in structure **1a**, is most stable. In analogy to cycloheptene, as well as several tetrathiepin and trithiepin analogs,[10,11] the process of ring inversion is proposed to involve an initial chair to boat transition, followed by pseudorotation through one of two enantiomeric twist-boat conformations to the new boat form, which, upon reversal of the first step, gives the opposite chair conformation. Next to the chair conformation, the most stable is the twist-boat (**1b**), approximately 8.7 kcal/mol higher in energy. However, of greater importance in the dynamics of the ring inversion is half-chair structure **1c**, which was calculated to be 34 kcal/mol higher in energy than the chair conformation.[12] This conformation, which has all five sulfur atoms within a single plane, is proposed to be the transition state between the chair and boat conformations.



1a **1b** **1c**

These calculations are consistent with *ab initio* molecular orbital calculations performed on theoretical parent compound 1,2,3,4,5-pentathiepin (**5**) by Chenard and co-workers.[11] The authors proposed the ring inversion process described above, based on an extensive dynamic NMR study of 1,2,4,5-tetrathiepin analog **6**.



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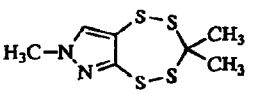

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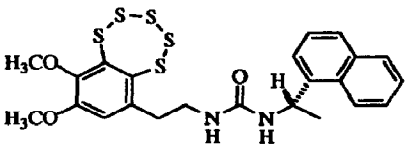
Their results also suggested that a chair should be the most stable conformation for **5**, and that the twist-boat and boat conformations would be approximately 4.5 and 14 kcal/mol higher in energy, respectively. The half-chair transition state for **5** was calculated to be 29 kcal/mol higher in energy than the chair. The presence of the benzene ring with substituents at the positions adjacent to the pentathiepin ring in varacin may account for the increased barrier to inversion relative to compound **5**.[11]

Although the calculated energy barrier, which is consistent with our variable temperature NMR results, should provide sufficient conformational stability to allow the direct separation of enantiomers, our attempts to accomplish this have been unsuccessful. Therefore, in an attempt to generate diastereomers, we treated varacin (**1**) with (*S*)-(+)-1-(1-naphthylethyl) isocyanate in dichloromethane in a sealed tube at 160 °C for 1 h, resulting in the formation of urea **7**. The ^{1}H NMR spectrum of **7** (Figure 2A) clearly showed doubling of the signals assigned to varacin's lone aromatic proton (~6.8 ppm) and the methoxy groups, together with slight doubling of some of the naphthalene ring signals (~7.5 ppm), indicating that diastereomeric products had been formed. Repeated crystallization of the mixture from $CHCl_3$ provided two



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fractions, one of which was shown by ^{1}H NMR to be essentially a single diastereomer (Figure 2B) while the other was enriched in the other diastereomer to a ratio of approximately 3:1. These results clearly demonstrate that chair-chair interconversions of the pentathiepin ring do not rapidly occur at room temperature.

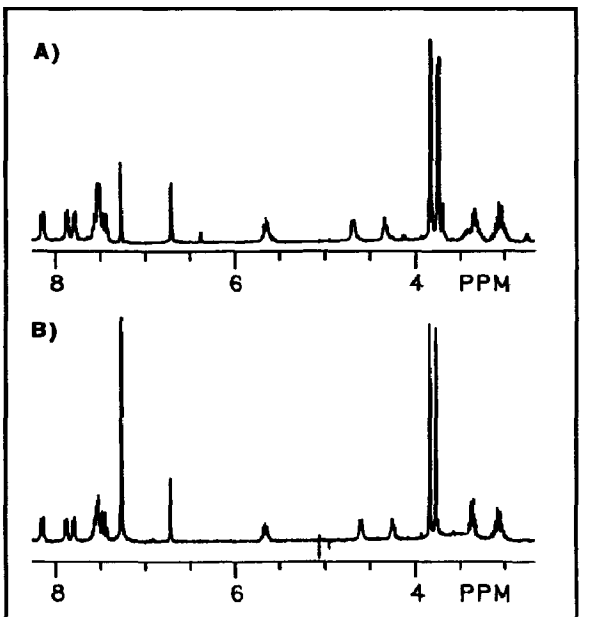

Figure 2. Partial ^{1}H NMR of (A) the diastereomeric mixture of compound **6**; (B) a single diastereomer of compound **6** after recrystallization from $CHCl_3$. Both spectra recorded in $CDCl_3$ at 300 MHz.

Our observation of unusually complex signals in the ^{1}H NMR spectrum of varacin (**1**) has led to the investigation of a chemical property which was unexpected for this class of compounds: *Chirality*. In this communication, we provide evidence indicating that unsymmetrically substituted benzopentathiepins are chiral because of a high activation barrier to interconversion of the low energy chair conformations. Therefore, varacin and its analogs provide new examples of molecules which are asymmetric because they contain a chiral plane.

Several questions remain to be answered. For example, how conformationally stable is the benzopentathiepin ring? We have observed slow interconversion at room temperature over a matter of days in deuteriochloroform; however, samples stored as a solid appear to be stable. It is also of interest to determine whether a sample of a benzopentathiepin, such as varacin, isolated from the natural source exists as a single enantiomer, and what affect this might have on the biological activity of the compound.

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12. The geometry of the transition state was simulated by holding the dihedral angles S1-S2-S3-S4 and S2-S3-S4-S5 at 0° by applying a 1000 kcal/rad^2 rotational force constant and then subjecting the resulting structure to the minimization-molecular dynamics-minimization routine described in reference 8.

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