change also brought about a structure with a lower energy.

It has been found that the antibiotic activity decreases with progressive dechlorination.[19] As noted above chlorines impart lipophilicity to the antibiotic molecule, perhaps helping the transmembrane transport in the target pathogens. As far as the binding interaction between the glycopeptide core and the L-Lys-D-Ala-D-Ala residue is concerned, no chlorine substituent of 1, with exception of A3 chlorine, appears to have a direct steric or hydrophobic effect, since all three chlorines at C3, A5, and F2 reside in the opposite side of the presumed interactions. It seems, however, likely that the presence of chlorine substituents may provide a certain degree of conformational rigidity to the glycopeptide framework, which is beneficial to the binding interaction.

Experimental Section

General. Analytical HPLC was performed on a Spectra-Physics 8100/4000 liquid chromatograph using 7–34% acetonitrile in 0.01 M KH_2PO_4 buffer (pH 3.2) and detection at 220 nm. A Beckman Ultrasphere ODS column (4.6 × 150 mm, at flow rate 1.5 mL/min) was used for the analytical runs. Preparative HPLC was carried out on a Whatman Magnum 20 (Partisil 10/ODS-3) column hooked up to an Eldex pump by running step gradient of 0–16% acetonitrile in 0.01 M KH_2PO_4 buffer (pH 6.0) at flow rate of 25 mL/min. Mass spectra were obtained with a VG Analytical ZAB-1F mass spectrometer equipped with a high-field magnet and operated in the fast-atom-bombardment mode with thioglycerol–oxalic acid matrix.

A Representative Reductive Dechlorination. A solution of aridicin aglycon (1, 210 mg) in 100 mL of distilled water (pH adjusted to 8.1 with dilute NH_4OH) was hydrogenated in a Parr hydrogenator over Pd/C (10%, 200 mg) at 60 psi H_2 and room temperature. Progress of the dechlorination was monitored by taking samples, filtering through Celite, and directly analyzing by HPLC as described above. After 140 min, all starting material disappeared, and the catalyst was removed by filtration through Celite (Aldrich). Lyophylization of the filtrate gave ca. 167 mg of powder, from which the following products were isolated through preparative HPLC: **2** [20 mg; t_r 12.86 min; FAB-MS, m/z 1262 (MH^+)]; **3** [10 mg; t_r 12.22 min; FAB-MS, m/z 1228 (MH^+)]; **4** [27 mg; t_r 11.08 min; FAB-MS, m/z 1228 (MH^+)]; **5** [52 mg; t_r 10.37 min; FAB-MS, m/z*1194* (MH^+)]; **6** [2 mg; t_r 9.51 min; FAB-MS, 1160 (MH^+)]. The parent aglycon **1** showed t_r 14.21 min and m/z 1296 (MH^+) under identical conditions. Isoelectric point of **1–6** were measured as previously described[6] and found to be in the 4.9–5.0 range.

NMR Spectroscopy. Samples were dried by lyophilization and prolonged pumping in the presence of P_2O_5. Approximately 2 mg of each powder was dissolved in 0.5 mL of freshly opened deuteriated solvents (100% D: Me_2SO-d_6/D_2O, 1/1). Proton spectra were obtained on a JEOL GX500 spectrometer at 500.1 MHz. All 2D NMR data were transferred to a VAX 11/780 via magnetic tape and processed with software developed by D. Hare.[20]

Chemical shifts and coupling constants were measured from Gaussian-enhanced spectra according to the algorithm in the JEOL NMR software. The line broadening factor was −4.0 Hz: Gaussian factor = 1.8 Hz; points = 16K; scans = >500; F_2 width = 5500 Hz. The internal reference was the Me_2SO signal (δ 2.49).

Details of the pulse sequences and phase cycling used for the COSY[21] and phase-sensitive 2D NOE experiments[22] were described at length elsewhere.[4] In this work, the following conditions were utilized. The temperature was maintained at 40 °C. In the COSY pulse sequence, the initial interval was 10 ms. The F_1 and F_2 spectral widths were set to approximately 3400 Hz. Sampling points (2K) were recorded in t_2 in the quadrature phase detection mode and 512 FID's (zero-filled to 1K) were taken in t_1 (32 scans each). Sine-bell apodization was applied before the Fourier transformation. An absolute value spectrum was calculated.

All 2D NOE spectra were calculated in the phase-sensitive mode by using the method of States et al.[22] In these experiments two FID's were collected for each t_1 value. These differed by 90° in the relative phase of the pulse between the evolution and mixing periods. To further suppress magnetization transfer due to J coupling, a homogeneity spoiling pulse was applied during the mixing period.[23] In spectra obtained from Me_2SO/D_2O samples, the residual water signal was suppressed by presaturation. The spectral width was approximately 3400 Hz in both time domains (16 scans per t_1 value). F_2 contained 2K points with 512 t_1 points recorded (zero-filled to 1K). The variable evolution interval initiated at 0.01 ms followed by a mixing time of either 250 or 500 ms. No sine-bell enhancement was used. The t_1–FID's were subjected to cosine apodization prior to Fourier transformation to avoid truncation effects in the 2D spectra. The final matrices were not symmetrized.

Molecular Modeling. The tridechloroaridicin aglycon **5** model was built from the starting geometry of the aridicin aglycon model whose construction has been described in detail.[4] The modifications were carried out in an Evans and Sutherland PS300 graphics system linked to a VAX 11/780 computer and energy minimization carried out as previously described.

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Registry No. **1**, 101630-74-4; **2**, 106947-57-3; **3**, 106947-58-4; **4**, 107033-40-9; **5**, 106947-59-5; **6**, 106947-60-8.

Supplementary Material Available: Tables of scalar and NOE connectivity and the aromatic regions of the COSY spectra for compounds **1–6** and the resolution-enhanced aromatic region of the ^1H NMR spectra of compound **6** (5 pages). Ordering information is given on any current masthead page.

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Acid-Mediated Trans-Cis Isomerization of Substituted Tetrathiafulvalenes. Selective Precipitation of the Trans Isomer

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We recently showed that unsymmetrically substituted tetrathiafulvalenes (TTF)[1] are readily generated by quantitative coupling of 4-thioxo mesoionic 1,3-dithiols. It was found that this reaction only gave the trans isomers as demonstrated by a single-crystal X-ray analysis.[2]

In this paper we report on ^1H NMR study, giving evidence for the first time of an acid-catalyzed trans–cis isomerization of the TTF core prior to the selective pre-

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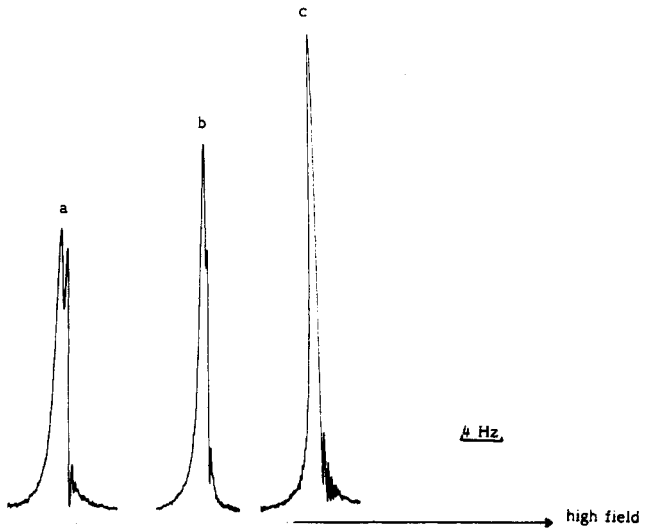


Figure 1. NMR spectra of TTF 1, SMe peak: (a) 0.6 g of 1 dissolved in boiling commercial $CDCl_3$ with 10 drops of C_5D_5N added, spectra recorded before any precipitation; (b) remaining filtrate after removal of the precipitate formed upon ice bath cooling (2 cis-rich solution), observed only if the spectra is immediately recorded; (c) peak observed for the precipitate in a CCl_4 solution (1 trans isomer).

cipitation of the trans isomer.

The thiomethyl group in 1 exhibits a particularly well-resolved singlet at 2.25 ppm in either CCl_4, C_6D_6, C_5D_5N, or basic alumina $CDCl_3$ purified. However, two signals were observed when these solvents were slightly acidified by gaseous HCl or when commercially available $CDCl_3$ was used without further purification.

These results can be explained by an isomerization of the trans TTF 1 catalyzed by H^+.

$$\text{TTF 1 (trans)} \overset{H^+}{\rightleftharpoons} [\text{TTF}]H^+ \overset{-H^+}{\rightleftharpoons} \text{TTF 2 (cis)}$$

In agreement with such equilibria two signals were observed when TTF 1 (trans) was first dissolved in commercial $CDCl_3$ (rapid isomerization) and then pyridine added, while only one signal was present when the TTF 1 (trans) was dissolved into a previously prepared mixture of $CDCl_3$ and pyridine. However, after a few minutes the second signal appeared, showing that the rate of isomerization was slowed by addition of pyridine but not eliminated.

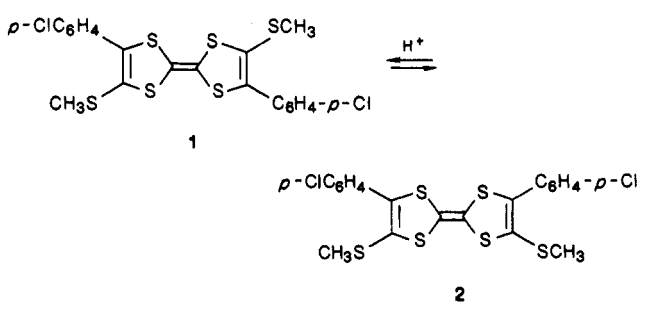
The second methyl peak does not arise from the protonated intermediate because when the isomerization was achieved, the relative intensity of the two methyl peaks was independent of the acidity of the medium. For instance, the two methyl peaks observed in a weakly acidic $CDCl_3$ solution of TTF 1 were not modified by further addition of pyridine, even after 1 h.

Another noteworthy feature of the TTF solutions is the selective precipitation of the trans isomer from saturated solutions. It was not possible to isolate the cis isomer even when pyridine was added *after* isomerization of the trans isomer (Figure 1a); cooling the solution afforded a precipitate of pure solid trans isomer 1 (Figure 1c) and a solution in which the cis isomer was the major compound (Figure 1b). However, the cis–trans equilibrium was too rapidly established to permit isolation of the cis TTF 2. After concentration of the solution, the trans isomer 1 was quantitatively recovered and identified on the basis of identical melting points as well as IR and NMR spectra.

Experimental Section

TTF 1 was selected because the thiomethyl group exhibits a well-resolved ^1H NMR signal. It was prepared according to the published procedure, and its physical data were as expected.[1] ^1H NMR spectra were recorded at 80 MHz on a Brüker WP 80 spectrometer. An expanded scale was used (2 Hz/cm^{-1}), and Me_4Si was the internal standard. The thiomethyl group signal is shifted upfield by about 5×10^{-3} ppm (Figure 1). Each experiment was repeated at least three times in order to avoid artifacts.

Scheme I



To show that isomerization was linked to the acidity of the medium, two final solutions were prepared in two different ways:

(a) A 0.5-g portion of 1 was first dissolved in 0.5 mL of commercially available $CDCl_3$ followed by addition of 10 drops of C_5H_5N; two methyl peaks were observed.

(b) A 0.5-g portion of 1 was dissolved in a previously prepared mixture of 0.5 mL of commercial $CDCl_3$ and 10 drops of C_5H_5N.

A single methyl peak was observed when the spectrum was immediately recorded, but two peaks appeared after a few minutes and equilibrium was reached after 40 min (identical spectra for a and b solutions).

The configuration of TTF 1 in the solid state was determined by an X-ray single-crystal structure determination. A reddish needle-shaped crystal ($0.40 \times 0.12 \times 0.04$ mm) was mounted on a Nonius CAD4 automatic diffractometer (graphite-monochromated Mo Kα radiation, θ–2θ scan technique). Data: monoclinic; space group $P2_1/n$; a = 8.994 (4), b = 25.343 (7), c = 4.821 (3) Å; β = 98.70 (5)°; V = 1086 Å^3; Z = 2, d_{calcd} = 1.583 g·cm^{-3}.

A total of 2780 independant reflections were collected up to θ = 28° of which 961 with $I > 3\sigma(I)$ were considered observed and included in the refinement. The structure was solved by direct methods and difference Fourier synthesis. Full-matrix least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms (with the hydrogen atoms included in fixed calculated positions) converged to R = 0.064 and R_w = 0.070. The asymmetric unit consists of a half molecule located on a center of symmetry. Accordingly, the thiomethyl groups are trans to each other as verified by the full-structure determination.

A Novel Synthesis of Selenium-Containing Heterocyclic Compounds. Carbonylation of Ortho-Substituted Anilines with Carbon Monoxide in the Presence of Selenium

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During the course of our study on selenium-assisted carbonylation with carbon monoxide,[1] we have found that

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