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Identification, Synthesis, and Conformation of Tri- and Tetrathiacycloalkanes from Marine Bacteria

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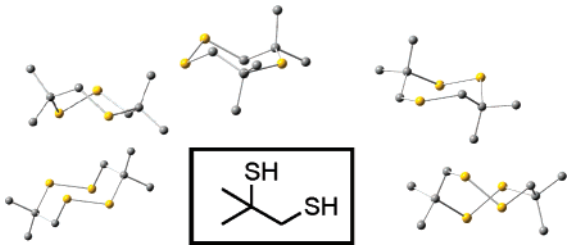
Received January 9, 2007



Seven new cyclic natural polysulfides **1**−**7** were identified in extracts of two bacterial *Cytophaga* strains (CFB-phylum) isolated from biofilms from the North Sea. Their structures are based on mono- and dimeric-cyclization products of 2-methylpropane-1,2-dithiol **8**, which was also present in the extract in trace amounts. The structures were deduced by analysis of their mass spectra and confirmed by synthesis. The ^{1}H NMR spectra of some these compounds suggested a high flexibility of the trithiepane and tetrathiocane systems. Therefore, their conformation was further analyzed by DFT calculations and dynamic NMR spectroscopy. While thiepane **4** possesses a twist-chair lowest energy conformation, its isomers **2** and **3** adopt a chairlike conformation, as does the tetrathiocane **5**. In contrast, tetrathiocane **6** favors again a twisted chair conformation.

Introduction

Marine microbial metabolites are currently intensively studied because of their often interesting pharmaceutical and agrochemical properties. Most of the research is focused on compounds of medium polarity, while apolar and volatile compounds have received less attention. In a research program aimed at the diversity of secondary metabolites from North Sea bacteria we developed a gas-chromatographic dereplication and strain selection method for fast identification of strains containing unknown apolar metabolites.[1] Two *Cytophaga* strains (BIO137 and BIO138), isolated from biofilms from the North Sea, were thus identified as potentially promising strains. The unknown compounds proved to be small sulfur-containing compounds. Volatile sulfur compounds play an important role in the global cycle of sulfur, including acidic rain, cloud formation, and in climate regulation.[2−6] Furthermore, they contribute to the aroma of fermented foods.[7,8] Nevertheless, the known volatile sulfur compounds from bacteria are limited.[9] In the present article we describe the identification, synthesis, and conformational analysis of new dithia-, trithia-, and tetrathiacycloalkanes produced by the *Cytophaga* bacteria.

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10.1021/jo070048w CCC: $37.00
Published on Web 04/12/2007

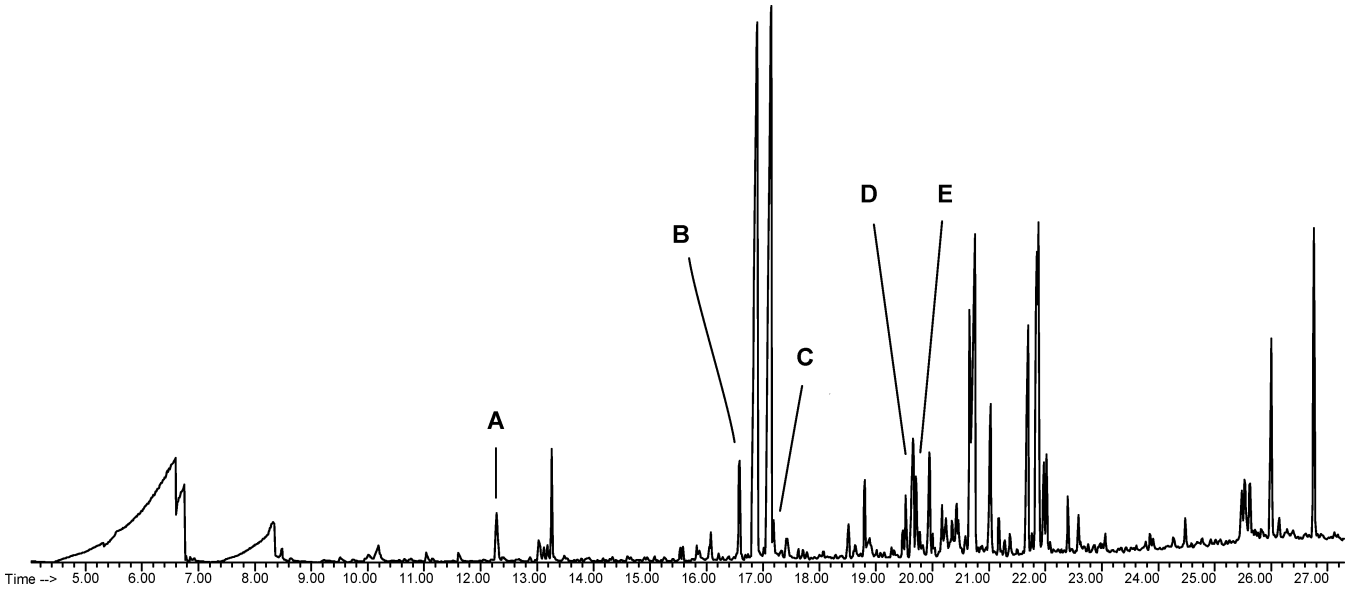

FIGURE 1. Gas chromatogram of *Cytophaga* strain BIO137 from the North Sea.

Results and Discussion

Identification. In general, the unknown compounds were identified by GC-MS analysis and interpretation of their mass spectra. To verify theses proposals, they were synthesized and compared to the natural compounds. Thus, the GC-MS analysis of the *Cytophaga* strains BIO137 and BIO138 revealed the presence of five small peaks containing sulfur (Figure 1), identifiable by the suspicious $M^+ + 2$ isotope peak in their mass spectra. These compounds **A**−**E** showed gas chromatographic retention indices of 1175, 1472, 1516, 1727, and 1748, respectively. The molecular formula was determined by GC-HRMS analysis, resulting in $C_4H_8S_3$ for **A**, $C_8H_{16}S_3$ for **B** and **C**, and $C_8H_{16}S_4$ for **D** and **E**, each with one double bond equivalent. It has to be noted that the strains were repeatedly fermented and always showed the presence of the sulfur compounds, while other strains cultured under exactly identical conditions did not contain these compounds. An anthropogenic source of the target compounds was thus excluded.

Mass spectrometrical data of several cyclic polysulfides have been published,[10−20] giving hints to the preferred mass spectrometric fragmentation of the unknown compounds. These data allowed us to make structural proposals for the compounds **A**−**E**. The mass spectrum of compound **A** contained characteristic ions at *m*/*z* 96 $[S_3]^{+\cdot}$, 55 $[C_4H_7]^+$, and 87 $[C_4H_7S]^+$, pointing to a sulfur triad, four connected carbon atoms, and a monocyclic structure (Figure S1). The presence of a small ion *m*/*z* 106 $[M - CH_2S]^{+\cdot}$ suggested a CH_2S fragment in the structure, while the prominent ion *m*/*z* 87 $[C_4H_7S]^+$ pointed to a $CH(CH_3)_2S$ or $CH(C_2H_5)S$ substructure. The latter one seemed to be less likely because no evidence for an ethyl group could be found in the mass spectrum. Furthermore, the published spectra of 3,5-dimethyl-1,2,4-trithiolane[14] and 3-ethyl-1,2,4-trithiolane[17] showed distinct differences, supporting the view of a sulfur triad. Therefore, we proposed compound **A** to be 4,4-dimethyl-1,2,3-trithiolane (**1**), which was proven by synthesis (see below). The two isomeric compounds **B** and **C** obviously contained an additional C_4H_8 group compared to **1** but no sulfur triad (Figure 2). Both C_4H_8 units were not connected directly, but via a S-atom. This can be deduced by *m*/*z* 143 $[C_8H_{15}S]^+$ and the absence of any CH containing fragment with more than four C-atoms. The C_4H_8 units are most likely again arranged in a dimethylethyl fashion, because in cyclic oligosulfides with longer alkyl side chains such as 3,5-dipropyl- or diisopropyl-1,2,4-trithiolane[16,17,20] no strong $[M - C_4H_8]^{+\cdot}$ ion (*m*/*z* 152) is formed. Instead, the intense $[M^+ - S_2H]^+$ fragment at *m*/*z* 143 prevails. Furthermore, the complete lack of $[M - C_nH_{2n+1}]^+$ ions indicates the absence of longer alkyl side-chains. The mass spectra of **B** and **C** were thus consistent with the structural proposals 4,4,6,6-tetramethyl-1,2,5-trithiepane (**2**), 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**), and 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**). Mieloszynski has published tabulated mass spectra of **2** and **3** isolated from undefined "mélanges industriels", showing the same ions as in our trithiepane mass spectra but in markedly different abundances. The reported ^{1}H NMR data of **2** were similar to ours obtained from a synthetic sample, while that of **3** differed.[10]

The mass spectra of compounds **D** and **E** contain the same fragments as **B** and **C** (except *m*/*z* 106), but obviously these compounds carry an additional S-atom, visible by the increase of 32 amu of the M^+ ion. Again, no S_3 fragment is observed, pointing to two disulfide bridges in the compounds. Therefore, 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (**5**) and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**) were proposed as target structures. The mass spectrum of **6** matches the literature data for

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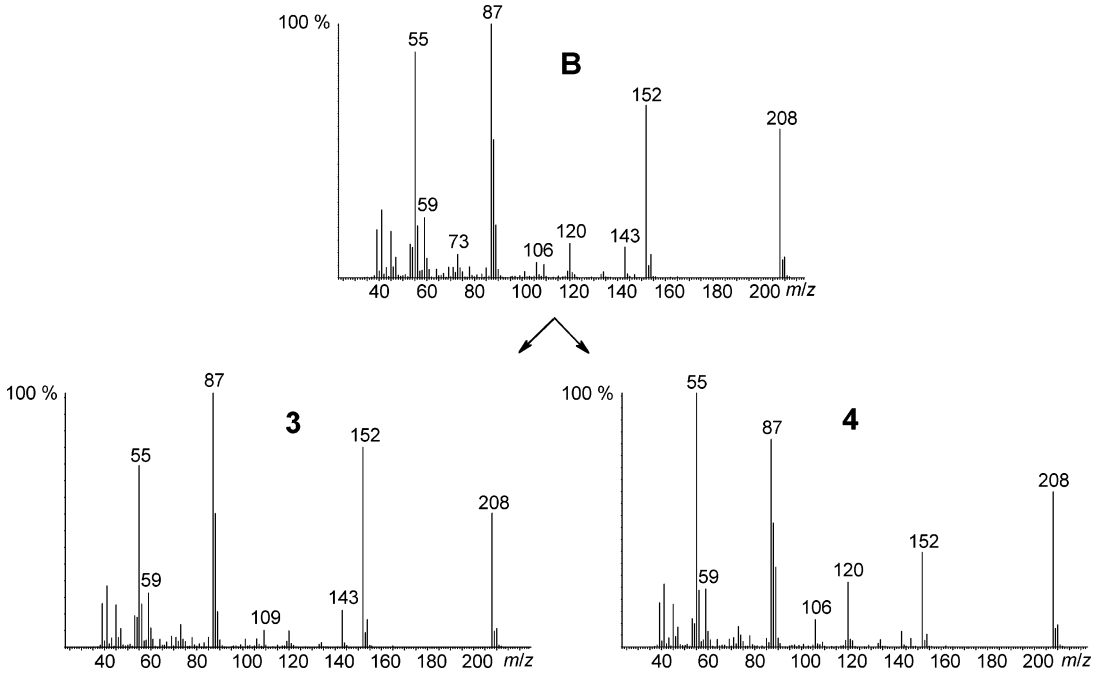
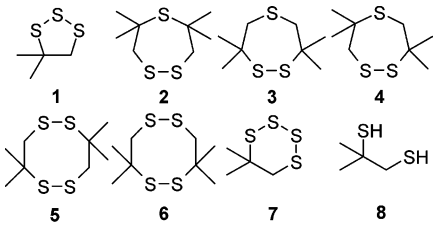


FIGURE 2. Mass spectrum of the peak B of the natural extract, composed of a 3:2 mixture of the two coeluting sulfides **3** and **4**.

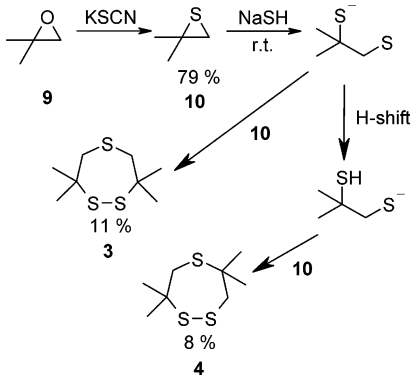
compound **5** by Mieloszynski, who suggested this structure but did not report NMR data.[10] A table of the GC-HRMS-data for the postulated structures **A**−**E** as well as mass spectra of compounds **1**−**2** and **5**−**8** are available in the Supporting Information.



Synthesis. Synthetic reference material was then needed to verify the proposed structures, to assign the potential isomers, and to obtain material for biotests. A first attempt of their synthesis was the nucleophilic thiolate ring opening of the episulfides. 2,2-Dimethyloxirane (**9**) was transformed with KSCN into 2,2-dimethylthiirane (**10**).[21] Then NaSH was added to **10** assuming that the SH^- nucleophile could attack the episulfide from the least hindered side, forming a thiolate anion which in turn should open another thiirane molecule, forming target compound **3** after a spontaneous oxidative ring-closing coupling of two sulfur atoms (Scheme 1). Compound **3** was isolated in 11% yield after extended chromatographic purification because of formation of many oligomeric side products. The isomeric thiepane **4** was also formed during the reaction and isolated in pure form; its formation can be rationalized by transfer of a proton from the primary to the tertiary sulfur position prior to the attack of the second thiirane molecule.

Compounds **3** and **4** were distinguished by their high-temperature NMR spectra. While **3** showed only one signal for the two methylene units, the spectrum of compound **4** was more

SCHEME 1. Synthesis of 3,3,7,7-Tetramethyl-1,2,5-trithiepane (3) and 3,3,6,6-Tetramethyl-1,2,5-trithiepane (4)



complex due to the missing symmetry plane. Interestingly, both compounds showed identical gas chromatographic retention times on an apolar BPX-5 phase. Careful analysis of the slight differences in the mass spectra of the synthetic products and **B** proved that **B** is actually a 3:2 mixture of **3** and **4** (Figure 2).

Because the above synthesis gave no access to the other compounds, an alternative strategy was used to synthesize the isomeric trithiepane **2** (Scheme 2).

The major product of the addition of sulfur monochloride and isobutene is 2-chloro-1-(2-chloro-2-methylpropyldisulfanyl)-2-methylpropane (**11**).[22] The following reaction with NaSH, which included the substitution of chloride, followed by a ring-closing reaction, led to **2** and **6**. By use of 1 equiv of NaSH, trithiepane **2** was isolated as major component, while tetrathiocane **6** was preferentially formed when 2 equiv was used. These compounds were always accompanied by the trithiolane **1**, which showed identical GC and MS data as compound **A**. Unfortunately, its isolation failed, presumably because of the known instability of trithiolanes.[23] The crude 4,4-dimethyl-1,2,3-

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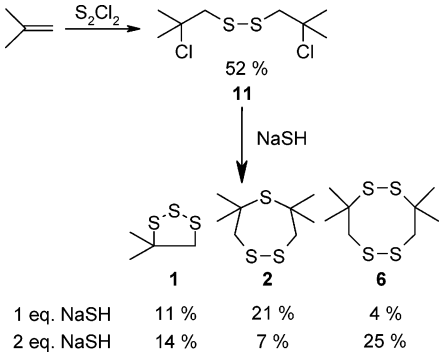
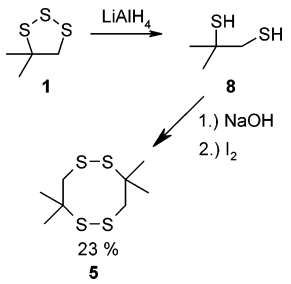
SCHEME 2. Synthesis of 4,4,6,6-Tetramethyl-1,2,5-trithiepane (2) and 3,3,8,8-Tetramethyl-1,2,5,6-tetrathiocane (6)



1 eq. NaSH	11 %	21 %	4 %
2 eq. NaSH	14 %	7 %	25 %

SCHEME 3. Synthesis of 3,3,7,7-Tetramethyl-1,2,5,6-tetrathiocane (5)



trithiolane (**1**) was then used as the starting material of compound **5** (Scheme 3).

LAH reduction of **1** furnished the dithiol **8**, which was oxidatively coupled with NaOH and iodine,[24] leading to 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**). This reaction sequence additionally proved the structure of **1**. Besides **6**, the compounds **1**, **4**, **7**, and 6,6-dimethyl-1,2,3,4,5-pentathiepane were formed as byproducts. These results suggested that the dithiol **8** might be involved in the biosynthesis of the sulfur cycles. Careful analysis of the GC-MS data revealed its presence in the natural extracts in trace amounts. Compound **8** is slowly oxidized when standing for longer periods in an open flask. All of the compounds **1**−**7** were formed, but in addition the opened dithiols of the trithiepanes and tetrathiocanes also occurred, while they were absent in the natural extracts. These results suggest that in the biosynthesis, **8** is formed first which is then autoxidized to compounds **1**−**7**, similarly as reported for the formation of dimethyl disulfide in bacteria.[25] We also tried to synthesize **1** by the addition of sulfur to isobutene, in analogy to the experiments of Bartlett and Ghosh with norbornene.[26] Small amounts of **1** were formed, but major components of the inseparable mixture were 5,5-dimethyl-1,2,3,4-tetrathiane (**7**) and 6,6-dimethyl-1,2,3,4,5-pentathiepane. Compound **7** proved to be identical to an additional trace component of the natural extract.

NMR Experiments. Compounds **2**−**6** showed interesting NMR spectra, pointing to considerable flexibility of the ring systems. Some ^{1}H NMR spectra at room temperature are presented in Figures 3 and 4. The spectrum of the symmetric

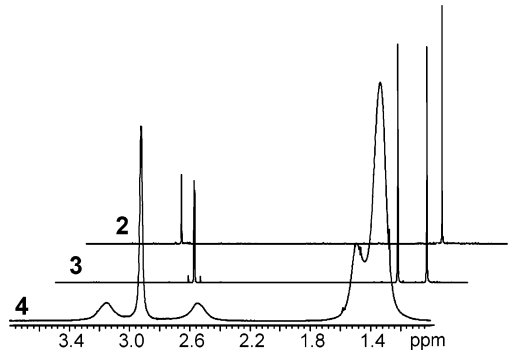


FIGURE 3. ^{1}H NMR spectra of the trithiepanes **2**−**4** at room temperature.

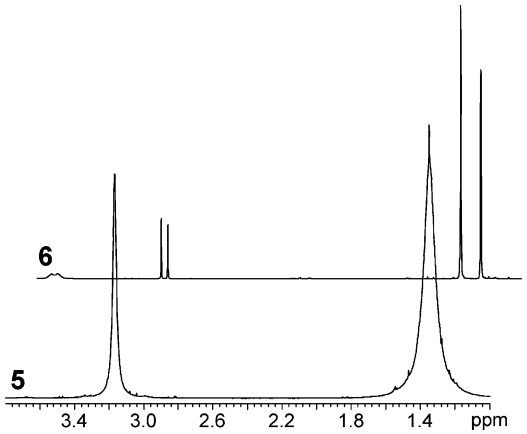


FIGURE 4. ^{1}H NMR spectra of the tetrathiocanes **5** and **6** at room temperature.

4,4,6,6-tetramethyl-1,2,5-trithiepane (**2**) showed only one signal for the four methyl and for the two methylene groups each, in contrast to the spectrum of 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**) in which two types of methyl groups can be differentiated. The protons of the methylene groups are also split into two doublets of an AB spin system. The spectrum of 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**) showed only broad signals, the point of coalescence being near this temperature. Obviously the flexibility of the trithiepanes at room temperature decreases from **2** to **4** and further to **3**. In case of the tetrathiocanes, similar spectra showed that **5**, again having a coalescence point near room temperature, is more flexible than **6** (Figure 4).

Then temperature-dependent NMR-experiments were performed to get more insight into the conformations of the thiepanes. As an example, the spectra for **4** are shown in Figure 5. At low temperature a preferred conformation exists which allows the observation of four different methyl groups and four different methylene-H atoms. In contrast, at high temperature only one signal for each of the two different methylene groups and each of the two different methyl groups was observed.

Conformations. In order to further analyze the conformational complexity and the dynamic properties due to rapid ring interconversion[27] in the thiepanes and thiocanes, we performed a series of DFT (density functional theory) gas-phase calculations. The resulting optimized conformations were then used as a starting point for GIAO (gauge independent atomic orbitals)[28] simulations of the corresponding NMR data in order

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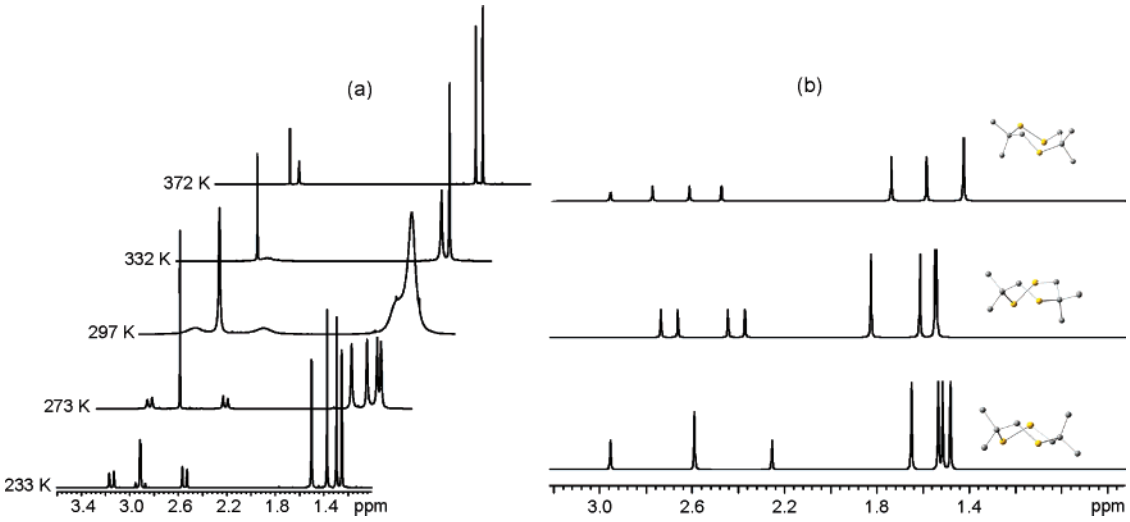

FIGURE 5. (a) Experimental ^{1}H NMR spectra of 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**) at different temperatures. (b) Simulated (DFT) spectra for the three calculated low energy conformations chair (upper trace), twist-boat (middle trace), and twist-chair (lower trace).

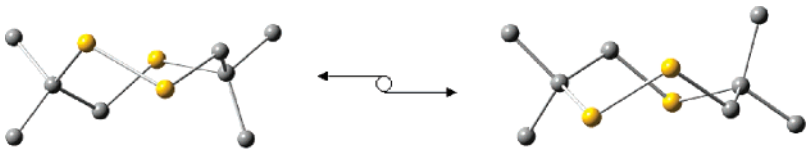

FIGURE 6. Interconversion of the two enantiomeric twist-chair global minima for 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**).

to characterize the dominating conformers. All calculations were done using the B3LYP[29] hybrid density functional in combination with a polarized triple-ζ basis set (6-311+G(d,p)). The procedure will be shown for 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**) as an example. In a first step, an extensive force field[30] scan of the energy surface was performed using the Macromodel 6.0 software package.[31] Second, all minima were reoptimized using the B3LYP functional. In the third phase, the energies and geometries of all transition states connecting the minima were localized and finally the NMR spectra for all energy minima were computed. Figure 6 shows the two conformers with the lowest energy, detected by this procedure. All quantum chemical calculations were done using the Gaussian 03 program.[32]

The interconversion of both low-energy twist chair conformations occurs via several chair, twist-boat, and chair conformations (Figure 7). Starting from the twist-chair minimum I (left), the next twist-boat minimum (6.2 kcal/mol) is reached via a boat transition state and separated by a barrier of 11.4 kcal/mol (back reaction: 5.3 kcal/mol), while the next transition structure (boat) is again 9.9 kcal/mol higher in energy (back reaction: 13.5 kcal/mol) leading to another minimum (chair), which is only 2.6 kcal/mol higher in energy compared to the twist-chair minimum I. Another transition state (8.7 kcal/mol; back reaction: 11.2 kcal/mol), best described as twist boat, has to be climbed before finally the twist-chair II minimum is reached. That means that the overall interconversion of the twist-chair conformations I and II occurs via two local minima and the activation barrier of the rate-determining step in the gas phase is predicted to be 13.5 kcal/mol. In order to find out if our theoretical findings hold also true for the condensed phase, we compared the simulated gas-phase ^{1}H NMR spectra for all characterized minima with the experimental low-temperature NMR spectrum of structure **4** in CD_2Cl_2 (Figure 5). The calculated spectra showed the relative positions of the methyl and methylene H atoms, omitting splitting due to coupling. It is obvious that the twist-chair conformation compares very well to the experimental spectrum, while the other two conformations showed marked differences. The experimental data supported the theoretical calculations and showed that in solution the twist-chair conformer is the most stable one.

To test this approach, the rate constant k_c for the interconversion of the twist-chair conformers was calculated according to formula I from the experimental ^{1}H NMR data. The difference in the frequency of two noncoupling signals from the ^{1}H NMR was measured ($\Delta\nu$, Table 1). In conjunction with the temperature of coalescence (T_c) the free activation enthalpy ΔG^{**} for this process was calculated according to formula II.[33]

$$k_c = \frac{\pi\Delta\nu}{\sqrt{2}} = 2.22\Delta\nu \text{ (I)}$$

$$\Delta G^{**} = 4.58T_c\left(10.32 + \log\frac{T_c}{k_c}\right) \text{cal mol}^{-1} \text{ (II)}$$

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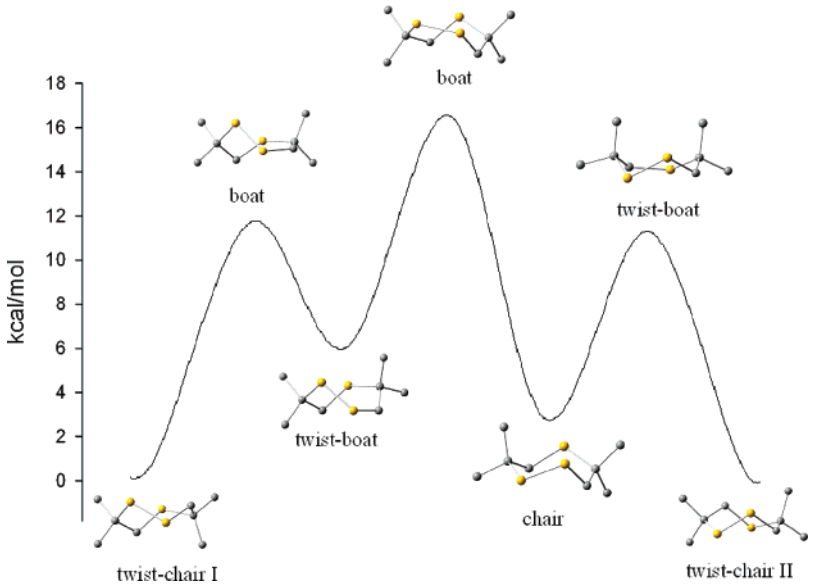

FIGURE 7. Conformational complexity of 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**). Stationary points were characterized at the B3LYP/6-311G-(d,p) level of theory. All optimized minima and transition state structures are included as xyz files in the Supporting Information.

TABLE 1. Frequency Difference of Methyl Groups in the ^{1}H NMR Spectra ($\Delta\nu$), Rate Constants (k_c), Temperatures of Coalescence (T_c), and Free Activation Enthalpies (ΔG^{**}) for the Interconversion Processes of Compounds 2−6

compd	$\Delta\nu$ (Hz)	k_c (1/s)	T_c (K)	ΔG^{**} (kcal/mol)
2	9.35	20.75	196	10.1
3	77.37	171.76	380	18. 6
4	82.61	183.39	288	13.9
5	91.71	203.59	293	14.1
6	46.09	102.31	-[a]	-

[a] The highest available experimental temperature was 373 K.

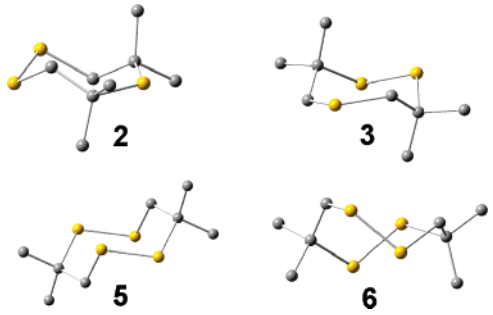

FIGURE 8. Calculated preferred conformations of compounds **2**, **3**, **5**, and **6**.

The thus obtained value of 13.88 kcal/mol is in good agreement with the theoretical result (13.5 kcal/mol), pointing to a good agreement of theory and experiment.

On the basis of the given procedure, the favored conformation of the trithiepanes **2** and **3** as well as the tetrathiocanes **5** and **6** were calculated (Figure 8). In addition, the rate constants, temperatures of coalescence and the free activation enthalpies for all interconversion processes were calculated (Table 1).

The free activation enthalpy for the interconversion processes of 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**) was theoretically calculated to be about 21 kcal/mol. That would match a coalescence temperature of about 420 K, which could not be measured on the given NMR equipment. All NMR data and MS spectra are available in the Supporting Information.

Conclusion

In the extracts of two *Cytophaga* strains from the North Sea the new thiacycloalkanes 4,4-dimethyl-1,2,3-trithiolane (**1**), 4,4,6,6-tetramethyl-1,2,5-trithiepane (**2**), 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**), 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**), 3,3,7,7-tetramethyl-1,2,5,6-tetrathiocane (**5**), and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane (**6**), and 5,5-dimethyl-1,2,3,4-tetrathiane (**7**) as well as the dithiol methyl-1,2-propanedithiol (**8**) were identified and their structures proven by synthesis. The cyclic compounds exhibit melting points between 34 °C and 106 °C have a characteristic smell resembling diesel-fuel. This smell can also be recognized in the extracts. The dithiol **8** has a penetrative, 'breathtaking' smell, obviously blocking the odor receptors for some time. The preferred conformations of the oligosulfides **2**−**6** can be well predicted using DFT calculations. In case of the trithiepanes, the most stable conformation of **3** shows a 'chair' arrangement, as does **2**, the most flexible compound of the three. The 'twist-chair' conformation of **4** is also adopted by the tetrathiocane **6,** while **5** prefers again a 'chair' arrangement. One explanation could be that in a chair conformation two methyl groups of **4** and **6** would adopt a quasiaxial position to each other, which is not the case in the twisted chair I and II. Cyclic alkyl polysulfides have occasionally been reported from nature. 1,2,4,6-Tetrathiepane and 1,2,3,5,6-pentathiepane (lenthionine) were isolated from the mushroom *Lentinus edodes*[34] and together with 1,2,4-trithiolane from the red algae *Chondria californica*.[35] The first two compounds showed antibiotic activity, while our compounds **3**−**6** were not effective in antimicrobial assays performed by us. Zeeck described a variety of alkyl-substituted 1,2,4-trithiolanes, 1,2,4,5-tetrathianes, and 1,2,3,5,6-pentathiepanes in the hyperthermophilic archea *Thermococcus tadjuricus*,[15] but none of those carried a geminal dialkyl group. Other substituted compounds like 4-methyl-1,2,3-trithiolane, 5-methyl-1,2,3,4-tetrathiane, or different dimethyl-1,2,5-trithiepanes are known as thermal

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degradation products of alliin and deoxyalliin from Garlic.[36] Compound **3** was tested as an oil additive.[37] 1,2,3-Trithiolane was recently found by Rushdi and Simoneit who did reactions with CS_2 and oxalic acid solutions in stainless steel vessels at high temperature and pressure to get information about the origin of life.[38] A cyclic polysulfide of which conformational studies are well-known is 1,3,5,7-tetrathiocane. Its crystallographic data were published in 1972[39] and its detailed boat-chair interconversion in 1973.[40] Published studies of different types of cyclic trisulfides including NMR data and rate calculations[41] shows that the activation enthalpies obtained by us are in a good agreement.

Experimental Section

Biological material. The strains were isolated from biofilms grown on glass plates exposed to the North Sea at a depth of 30 cm for 14 days as described[42] and identified by 16S rRNA gene sequencing.

Synthesis of 2,2-Dimethylthiirane (10). This compound (bp 84−86 °C, 4.84 g, 55 mmol, 79% yield) was prepared according to the procedure of Snyder and Stewart[21] with KSCN (6.79 g, 70 mmol) in 7 mL of H_2O and 2,2-dimethyloxirane (5.04 g, 70 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.62 (s, 6H), 2.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 28.5(CH_3), 35.4(CH_2), 42.4-(C).

Synthesis of 3,3,7,7-Tetramethyl-1,2,5-trithiepane (3) and 3,3,6,6-Tetramethyl-1,2,5-trithiepane (4). In a three-necked round-bottom flask, 7 equiv of NaSH·xH$_2$O (21.56 g) was dissolved in 200 mL of MeOH, and triethylamine (0.56 g, 5.5 mmol) was added. Then 2,2-dimethylthiirane (4.84 g, 55 mmol) was added dropwise during 30 min. The solution was stirred at room temperature. After 2 days, water was added and the mixture extracted three times with diethyl ether. The solvent was removed after drying with $MgSO_4$ under reduced pressure. The obtained liquid was purified by column chromatography with pentane and 3,3,7,7-tetramethyl-1,2,5-trithiepane (**3**) (1.2 g, 5.8 mmol, 11%, R_f = 0.15) obtained as a pale yellow solid. Mp: 46 ± 0.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.27 (s, 6H), 1.47 (s, 6H), 2.81 (dd, J = 2.3, 17.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 27.0 (CH_3), 28.2 (CH_3), 50.2 (CH_2), 52.4 (C). IR [cm^{-1}]: 2952, 1443, 1360, 1139, 1093. Anal. calcd for $C_8H_{16}S_3$: C, 46.11%; H, 7.74%; S, 46.16%. Found: C, 45.86%; H, 7.34%; S, 45.91%. 3,3,6,6-tetramethyl-1,2,5-trithiepane (**4**) (0.9 g, 4.3 mmol, 8%, R_f = 0.12). Mp: 34 ± 0.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.33 (s_B, 12H), 2.55 (s_B, 1H), 2.92 (s, 2H), 3.15 (s_B, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 25.9(CH_3), 27.1(CH_3), 29.9(CH_3), 30.9(CH_3), 41.5(CH_2), 45.6(C), 55.6(C), 57.7(CH_2). IR [cm^{-1}]: 2957, 1441, 1375, 1137, 1093.

Synthesis of 2-Chloro-1-(2-chloro-2-methylpropyldisulfanyl)-2-methylpropane (11). Isobutene (5.6 g, 0.1 mol) was condensed into a round-bottom flask, cooled with liquid nitrogen, and than dissolved in dichloromethane at −40 °C. S_2Cl_2 (0.5 equiv, 6.75 g, 0.05 mol) was added and stirred for 60 min at −40 °C, followed by 2 h of stirring at room temperature. The solvent and the excess of S_2Cl_2 were separated by distillation. The obtained liquid was purified by column chromatography with pentane as solvent (12.8 g, 52 mmol, 52%, R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.67 (s, 12H), 3.65 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 31.3(CH_3), 56.7(CH_2), 69.0(C).

Synthesis of 4,4,6,6-Tetramethyl-1,2,5-trithiepane (2). The synthesized 2-chloro-1-(2-chloro-2-methylpropyldisulfanyl)-2-methylpropane (0.5 g, 2 mmol) was dissolved in MeOH (10 mL), and NaSH·xH$_2$O (0.11 g) was added in small portions. The solution was stirred at room temperature overnight and was then extracted with diethyl ether. The solvent was removed after drying with $MgSO_4$ under reduced pressure. The obtained liquid was purified by column chromatography with a 200:1 mixture of pentane and diethyl ether (0.1 g, 0.42 mmol, 21%, R_f = 0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.43 (s, 12H), 3.16 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 31.1 (CH_3), 52.7 (C), 57.4 (CH_2). IR [cm^{-1}]: 2959, 2921, 1457, 1409, 1377, 1362, 1101.

Synthesis of 3,3,8,8-Tetramethyl-1,2,5,6-tetrathiocane (6). NaSH·xH$_2$O (0.22 g) was dissolved in MeOH (10 mL), and 2-chloro-1-(2-chloro-2-methylpropyldisulfanyl)-2-methylpropane (0.5 g, 2 mmol) was added. The solution was stirred at room temperature over night and was extracted with diethyl ether. The solvent was removed after drying with $MgSO_4$ under reduced pressure. The obtained liquid was purified by column chromatography with Pentane as solvent (0.12 g, 0.5 mmol, 25%, R_f = 0.15). Mp.: 71 ± 0.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.23 (s, 6H), 1.34 (s, 6H), 3.06 (d, J = 15.2 Hz, 2H), 3.70 (d, J = 15.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 25.2(CH_3), 32.2(CH_3), 51.1-(C), 53.9(CH_2). IR [cm^{-1}]: 2953, 2896, 1377, 1358, 1090. Anal. calcd. for $C_8H_{16}S_4$: C, 39.96%; H, 6.71%; S, 53.34%. Found: C, 40.04%; H, 6.55%; S, 53.32%.

Synthesis of 2-Methyl-1,2-propanedithiol (8). The crude 4,4-dimethyl-1,2,3-trithiolane (1.5 g), coproduct in the synthesis of 4,4,6,6-tetramethyl-1,2,5-trithiepane and 3,3,8,8-tetramethyl-1,2,5,6-tetrathiocane, was added to a large excess of $LiAlH_4$ (2 g, 52 mmol) in absol diethyl ether. The solution was boiled at 45 °C for 3 h and hydrolyzed by addition of concd HCl until all solids dissolved. The aqueous layer was extracted several times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed. The crude product was finally purified by distillation to yield pure **8** (0.7 g, 5.7 mmol) (40−41 °C, 38 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.43 (s, 6H), 1.61 (t, J = 8.8 Hz, 1H), 2.02 (s, 1H), 2.75 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 30.25 (CH_3), 41.21 (CH_2), 45.12 (C).

Synthesis of 3,3,7,7-Tetramethyl-1,2,5,6-tetrathiocane (5). To a mixture of NaOH (0.4 g, 10 mmol) and KI (10 mg, 0.06 mmol), dissolved in H_2O (10 mL) and cooled in an ice-bath to 0 °C, was added 2-methyl-1,2-propanedithiol (0.6 g, 5 mmol) dropwise, and the solution was stirred for 30 min. Than I_2 (1.27 g, 5 mmol) was added portionwise until a light red color persisted. The solution was extracted with dichloromethane. After drying with $MgSO_4$, the solvent was removed under reduced pressure by column chromatography with pentane, yielding a pale yellow solid (0.26 g, 1.1 mmol, 23%, R_f = 0.1). Mp: 106 ± 0.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.35 (s_B,12H), 3.17 (s_B, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 56.3(C). IR [cm^{-1}]: 2953, 1450, 1363, 1134, 1091, 548.

Acknowledgment. Financial support was provided by the Volkswagenstiftung within the Marine Biotechnology Project in Lower-Saxony (Germany).

Supporting Information Available: The methods and instruments as well as the spectral data of the compounds **1**−**3**, **5**−**8**, **10**, and **11**, a table with the HRMS data of the compounds **A**−**E**, and XY data of calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070048W

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