Conformational Analysis in Multisulfur Heterocycles. VIII. 3,3:6,6-Bis(tetramethylene)-*s*-tetrathiane and 3,3:6,6-Bis(pentamethylene)-*s*-tetrathiane. Slow *s*-Tetrathiane Chair-to-Twist, Chair-to-Chair, and Twist-to-Twist Interconversions. X-Ray Crystallographic Studies

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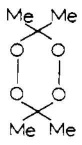
Abstract: Examination of the ^{1}H dnmr spectra of 3,3:6,6-bis(tetramethylene-*2,2,3,3*-d_4)-*s*-tetrathiane provided activation parameters for the *s*-tetrathiane twist to chair ($\Delta H^* = 14.7 \pm 0.5$ kcal/mol, $\Delta S^* = -3 \pm 2$ eu, $\Delta G^* = 15.7 \pm 0.1$ kcal/mol at 26.2°) and chair to twist ($\Delta H^* = 15.7 \pm 0.5$ kcal/mol, $\Delta S^* = -2 \pm 2$ eu, $\Delta G^* = 16.2 \pm 0.1$ kcal/mol at 26.2°) processes as well as clear evidence for an unusually high potential barrier to *s*-tetrathiane twist-to-twist interconversion ($\Delta H^* > 16$ kcal/mol). The ^{1}H dnmr spectrum of 3,3:6,6-bis(pentamethylene-*2,2,3,3,4,4*-d_6)-*s*-tetrathiane revealed changes consistent with slow *s*-tetrathiane chair-to-twist and twist-to-twist stereomutation as well as slow cyclohexane ring reversal. The dnmr data also provide accurate measurement of the chair:twist ratio in a number of *s*-tetrathianes. An X-ray crystallographic study of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane showed it to be triclinic, space group $P\bar{1}$, $a = 6.632$ (6), $b = 8.462$ (6), $c = 6.446$ (6) Å; $\alpha = 93.92$ (6)°, $\beta = 103.23$ (6)°, $\gamma = 96.90$ (6)°; $Z = 1$; $d_x = 1.396$ g cm^{-3}; $R = 0.025$ for 2715 nonzero reflections measured with a scintillation counter. In this crystal, the molecule is centric with all three rings in chair conformations. Average bond distances are S–S = 2.035 (2), C–S = 1.842 (2), and C–C = 1.525 (1) Å.

Since the early prediction by Sachse that cyclohexane could exist in the chair, boat, or twist conformations[2] and the later determination of the preference for the chair form by Hassel,[3] there have been extensive investigations of the conformational idiosyncrasies of the cyclohexane ring.[4] Theoretical calculations and experimental measurements indicate that the twist and boat forms of cyclohexane are at least 5 kcal/mol higher in energy than the chair.[5] Subsequent investigations of a large variety of saturated six-membered heterocycles indicate a general preference for the chair conformation[6] albeit somewhat distorted from a perfect chair in some cases.[7] Even the multiheteroatomic six ring acetone diperoxide (**1**)[8] and *N,N′,N″,N‴*-tetramethylhexahydrotetrazine (**2**) prefer the chair form, although **2** displays an unusual axial preference for two methyl groups.[9]



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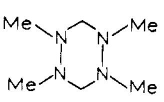

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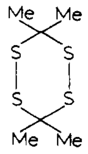
Studies of substituent conformational preference in a variety of six-membered heterocyclic systems revealed deviations from the cyclohexane analogs[10] as well as a marked dependence of substituent dynamics (*e.g.*, *tert*-butyl rotation) on the nature of the heterocycle.[11] In some cases, significant variations[12] in the rate of six-ring reversal as compared with cyclohexane[13] are observed.

In considering six-membered saturated sulfur-containing rings, there exists a general preference for the chair conformation,[14] although unusual substituent conformational biasing is sometimes observed.[6,10,15] The barriers for chair-to-chair equilibration in a variety of sulfur-containing six rings, including thiane (11.6 kcal/mol),[16] 1,2-dithiane (11.6 kcal/mol),[17] 1,2,3-trithiane (13.2 kcal/mol),[18] 1,3,5-trithiane (11.1 kcal/mol),[19] and pentathiane (>15 kcal/mol),[20] are usually comparable to or greater than that for cyclohexane (11.0 kcal/mol).[13]

In previous papers, we reported the results of ^{1}H dnmr studies concerning the stereodynamics and unusual ring conformational preferences in 3,3,6,6-tetramethyl-*s*-tetrathiane (**3**, "duplodithioacetone") and other *s*-tetrathianes.[21] The most striking difference between the *s*-tetrathianes and a host of saturated six-membered heterocycles is a drastically lowered *s*-tetrathiane chair-twist energy difference with the *twist favored* in **3**.



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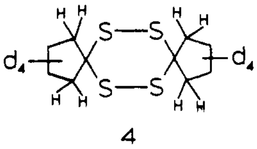
This report concerns an X-ray crystallographic study of the *s*-tetrathiane ring system and dnmr investigations of 3,3:6,6-bis(tetramethylene-*2,2,3,3*-d_4)-*s*-tetrathiane (**4**) and 3,3:6,6-bis(pentamethylene-*2,2,3,3,4,4*-d_6)-*s*-tetrathiane (**5**) revealing clearly an unusually high barrier to *s*-tetrathiane twist-to-twist interconversion.



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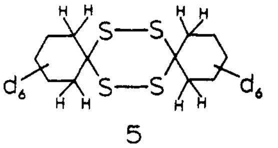

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Results and Discussion

For the purpose of dnmr spectral simplification, 3,3:6,6-bis(tetramethylene-*2,2,3,3*-d_4)-*s*-tetrathiane (**4**) was synthesized as shown in Scheme I. Examination of the ^{1}H dnmr spectrum (60 MHz) of **4** (10% by weight in CS$_2$) with irradiation at the ^{2}H resonance frequency revealed an exchange-broadened spectrum at 26.2° (Figure 1). When the temperature was lowered, the spectrum sharpened signifi-

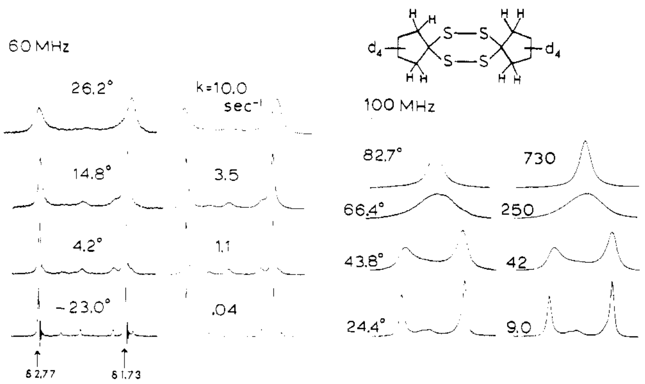
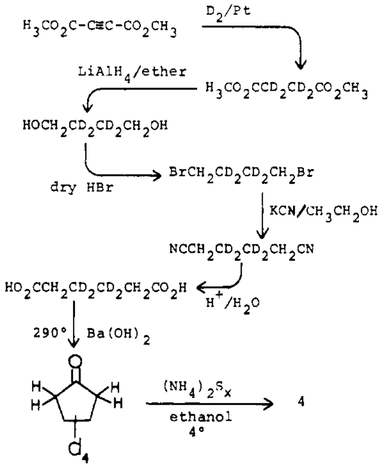
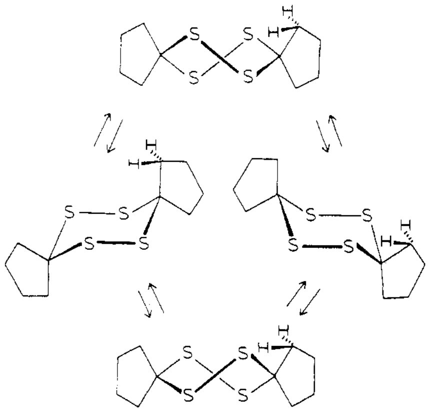


Figure 1. The experimental ^1H dnmr spectra of **4** at 60 MHz (10% by weight in CS_2) with irradiation at the ^2H resonance frequency and at 100 MHz (5% by weight in C_2Cl_4) without ^2H irradiation and theoretical spectra calculated as a function of the rate of *s*-tetrathiane chair–twist equilibration (k = first-order rate constant for conversion of the chair to the twist).

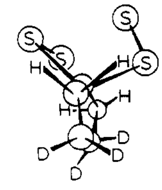
Scheme I



cantly, consistent with slowing a rate process on the dnmr time scale and giving two sharp singlets of equal intensity at δ 1.73 and 2.77 as well as an AB spectrum with components at δ 2.36 and 1.78 ($J_{AB} = -14.2$ Hz). The ratio of the total area of the two singlet resonances to the total area of the AB spectrum at −23° is 4.3:1.0. Subsequent examination of the 100-MHz dnmr spectra of **4** (5% by weight in C_2Cl_4) revealed essentially the same behavior except that the ratio of the two singlets to the AB spectrum is reduced to 3.5:1.0 at −16° presumably the result of a solvent effect. When the tetrachloroethylene sample was warmed, the ^1H dnmr spectrum (100 MHz) collapsed to a sharp single line at about 90° (Figure 1) consistent with a rate process which is rapid on the dnmr time scale. By analogy with previous dnmr data for **3**,[21f] the two large singlet resonances observed for **4** at −23° (Figure 1) can be assigned to the axial and equatorial CH_2 groups of the chair conformation of **4** (eq 1). Assuming fast pseudorotation of the cyclopentane ring in **4**, the two protons of a given CH_2 group in the *s*-tetrathiane chair will be equivalent because of C_{2h} symmetry of the tetrathiane chair form. The AB spectrum may then be assigned to the twist conformer of the *s*-tetrathiane ring (eq 1), but *the observation of an AB spectrum for the twist implies a unique dynamical situation.* Even in the event of fast cyclopentane pseudorotation in **4**, *slow s-tetrathiane twist-to-twist interconversion* will render the two protons of a given CH_2 group nonequivalent because of the D_2 symmetry of the *s*-tetrathiane twist and the proximate "up" or "down" sulfur-sulfur bonds. A projection looking down the CH_2-CS_2 carbon-carbon bond of a twist form (**4a**) illustrates the nonequivalent environments experienced by the two protons of a given methylene group. If the *s*-tetrathiane twist-to-twist process were fast on the dnmr time scale, the AB pattern for the twist would be time averaged to a single line. Thus, the dnmr spectra illustrated in Figure 1 are consistent with a preference for the *s*-tetrathiane chair form in **4** although the chair–twist energy difference is quite low. The spectra are also consistent with an unusually high potential barrier to *s*-tetrathiane twist-to-twist interconversion.



(1)



4a

A total dnmr line shape analysis was performed for **4** (Figure 1) using an expanded local version of DNMR3[22] (see Experimental Section). The chemical model used to simulate the dnmr spectra is that illustrated in eq 1, *i.e.*, no direct chair-to-chair or twist-to-twist equilibration. In this model, the chair is an intermediate in the twist-to-twist process, and the twist is an intermediate in the chair-to-chair process. Using this model, it is necessary to employ four molecular configurations (*i.e.*, two twist and two chair forms) with two nuclei in each configuration. DNMR3 was modified to accommodate this model (see Experimental Section). Theoretical dnmr spectra were then generated as a function of the rate of the chair-to-twist interconversion while taking into account small systematic variations in the chair:twist ratio and chemical shifts with temperature by extrapolation from low temperature data. Excellent agreement between experimental and theoretical spectra was obtained (Figure 1). Another model was tested in which increasing amounts of direct chair-to-chair and twist-to-twist conversion was introduced. Above about 10% direct chair-to-chair and twist-to-twist conversion, the deviation of the calculated spectrum from the experimental was marked particularly with regard to the width at half-height of the exchange-broadened CH_2 resonances of the chair form (*e.g.*, 24.4° in Figure 1). Thus, it might be concluded that direct chair-to-chair or twist-to-twist conversion is occurring at a rate much slower than the chair-to-twist process. By use of both the 60- and 100-MHz dnmr data, rate constants for the chair-to-twist equilibration were derived from the total line-shape analysis (Table I) and activation parameters for the chair-to-twist and twist-to-chair processes calculated (Figure 2; Table II).

Proceeding from the chair to the twist or the reverse involves essentially rotation about one of the S–S bonds. A

Table I. Rate Constants for Chair–Twist Equilibration in 3,3:6,6-Bis(tetramethylene-*2,2,3,3-d*$_4$)-*s*-tetrathiane (**4**) at Various Temperatures[a]

T, °C	k_{CT}, sec^{-1}	k_{TC}, sec^{-1}
82.7 ± 2.0[b]	730 ± 50	1460 ± 100
66.4 ± 2.0[b]	250 ± 30	500 ± 60
51.5 ± 1.8[b]	75 ± 5	143 ± 10
43.8 ± 1.5[b]	42 ± 3	84 ± 8
34.5 ± 1.0[b]	20 ± 2	46 ± 5
26.2 ± 0.3[c]	10 ± 1	22 ± 3
24.4 ± 1.0[b]	9.0 ± 1.0	23 ± 2
19.0 ± 0.3[c]	6.0 ± 0.7	15 ± 1
14.8 ± 0.3[c]	3.5 ± 0.2	9.5 ± 0.6
10.6 ± 1.0[b]	2.0 ± 1.0	5.0 ± 2.0
10.1 ± 0.3[c]	2.3 ± 0.4	6.7 ± 0.6
4.2 ± 0.3[c]	1.1 ± 0.3	4.5 ± 0.6
−1.6 ± 0.3[c]	0.5 ± 0.2	2.0 ± 0.6
−2.5 ± 1.0[b]	0.5 ± 0.5	1.6 ± 0.7
−6.8 ± 0.3[c]	0.3 ± 0.3	1.2 ± 0.8
−10.7 ± 0.3[c]	0.2 ± 0.2	0.8 ± 0.6

[a] k_{CT} = first-order rate constant for conversion of the chair to the twist; k_{TC} for twist to chair. [b] 100 MHz in C_2Cl_4. [c] 60 MHz in CS_2.

Table II. Activation Parameters for Chair–Twist Equilibration in 3,3:6,6-Bis(tetramethylene-*2,2,3,3-d*$_4$)-*s*-tetrathiane (**4**)

Process	ΔH^*, kcal/mol	ΔS^*, eu	ΔG^*, kcal/mol (26.2°)
Chair to twist	15.7 ± 0.5	−2 ± 2	16.2 ± 0.1
Twist to chair	14.7 ± 0.5	−3 ± 2	15.7 ± 0.1

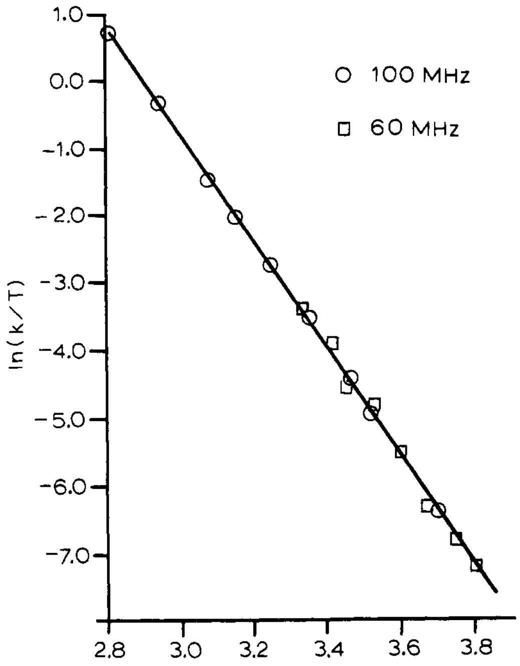


Figure 2. Plot of ln (k/T) *vs.* $1/T$ (least-squares fit) for the chair-to-twist process in **4** using data at 60 MHz and 100 MHz.

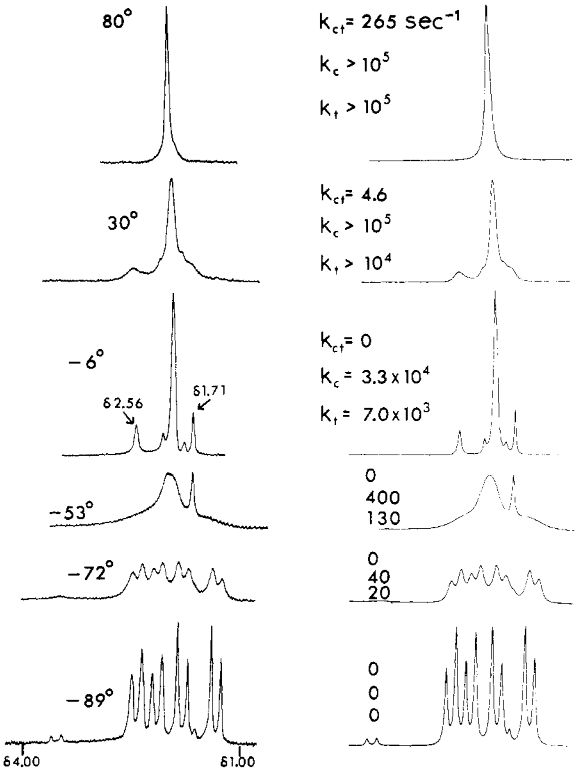
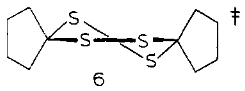


Figure 3. The ^{1}H dnmr spectra (100 MHz) of **5** as a function of temperature in C_2Cl_4 (80 to 30°) and CS_2 (−6 to −89°) and theoretical spectra calculated as a function of the rate of the *s*-tetrathiane chair-to-twist (k_{ct}) process and cyclohexane ring reversal in the *s*-tetrathiane chair (k_c) and twist (k_t). A rate constant of zero does not imply an absolute rate constant of zero but merely that the rate process is now slow enough not to affect the dnmr spectrum.

reasonable transition state for such a process would be the half-chair form **6**. The high potential barriers for these processes (Table II) seem reasonable in light of the relatively high apparently cis barriers to rotation about the S–S bond in acyclic disulfides (ΔH^* ~ 9 kcal/mol)[23] in addition to the angle strain in **6**.



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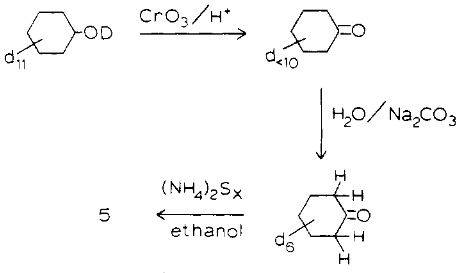
It should be noted at this point that the dnmr spectra illustrated in Figure 1 do not show a separate series of changes as a function of temperature attributable to slowing the *s*-tetrathiane twist-to-twist process. Indeed, it is apparent that the twist-to-twist process proceeds *via* the chair as an intermediate (eq 1). Thus, the barrier to the twist-to-twist process in **4** must be at least 16 kcal/mol which is remarkably larger than the analogous process in the cyclohexane twist (ΔH^* ~ 1 kcal/mol),[24a] although a high barrier for twist-to-twist interconversion has been claimed in the encumbered 1,2-*cis*-di-*tert*-butylcyclohexane.[24b]

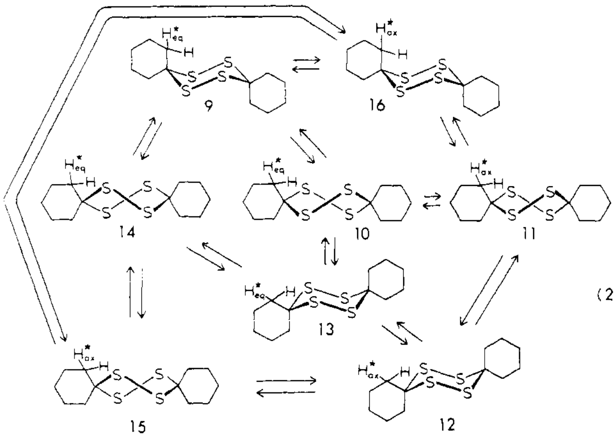
For the purpose of dnmr spectral simplification, 3,3:6,6-bis(pentamethylene-*2,2,3,3,4,4-d*$_6$)-*s*-tetrathiane (**5**) was synthesized as shown in Scheme II.

Scheme II



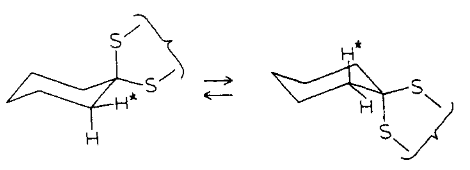
Examination of the ^{1}H dnmr spectrum (100 MHz) of **5** (10% by weight in C_2Cl_4) without ^{2}H irradiation at 80° (Figure 3) revealed a singlet resonance consistent with all protons in **5** rendered equivalent because of a rate process which is rapid on the dnmr time scale. Upon lowering the temperature to 30°, the spectrum collapsed in an asymmetric fashion (Figure 3). Subsequent examination of the ^{1}H dnmr spectrum (100 MHz) of **5** (8% by weight in CS_2) at

−6° (Figure 3) revealed two singlet resonances of *equal area* albeit different widths at half-height at δ 1.71 and 2.56 and by analogy with previous data for 3^{21f} and **4** discussed herein, these two singlets may be assigned to the axial and equatorial CH_2 groups of the *s*-tetrathiane chair form of **5** (eq 2). In addition to the singlet resonances at δ 1.71 and 2.56, there is a dominant *apparent* singlet at δ 1.97 flanked by two very small peaks of *different* relative intensities. When we first examined the ^1H dnmr spectrum of 5^{21g} at about −6°, the large *apparent* singlet was assigned correctly to the twist form (eq 2) by analogy with 3^{21} and **4**, but in the absence at that time of a complete line-shape analysis to be described below, this *apparent singlet* for the twist and the *different relative intensities* for the two very small peaks immediately flanking the dominant twist resonance led us to conclude erroneously that these two very small signals were due to impurities. Consequently, these two resonances were subtracted from the spectrum at −6° in our original communication.[21g] Somewhat to our chagrin, a subsequent total dnmr line-shape analysis for **5** at −6° to be described below revealed these two peaks to be the outer two lines of a closely spaced AB spectrum with one AB component differentially exchange-broadened, thus leading to different relative intensities. The two inner lines of the AB spectrum nearly coincide, giving the apparent singlet. However, in a manner completely analogous to other *s*-tetrathianes,[21] changes in the dnmr spectra of **5** from 80 to −6° may be attributed to slowing the *s*-tetrathiane chair–twist equilibration.



(2)

At −6° (Figure 3), cyclohexane ring reversal in **5** should be rapid enough on the dnmr time scale not to affect the dnmr spectrum significantly, although it is apparent that the small singlet at δ 2.56 is differentially exchange broadened. At lower temperatures, complex changes occur. The two small singlet resonances due to the *s*-tetrathiane chair at δ 1.71 and 2.56 broaden substantially and each separates respectively into an AB spectrum of which one component (δ 3.53, $J_{AB} = -13.5$ Hz) is observed at −89° (Figure 3) with the remaining components obscured by the dominant twist resonances. The twist resonance has separated at −89° into *two separate AB spectra* (δ 2.43, 1.81, $J_{AB} = -13.5$ Hz; and δ 2.16, 1.35, $J_{AB} = -13.5$ Hz). These dnmr spectral changes from −6 to −89° (Figure 3) are best rationalized in terms of slowing cyclohexane ring reversal in **5** (eq 3). However, the observation of *two* separate AB spectra for the tetrathiane twist conformer of **5** under conditions of slow cyclohexane ring reversal implies again a unique dynamical situation. Considering the cyclohexane chair form in the *s*-tetrathiane twist conformer of **5**, it would be expected that syn-axial nonbonded repulsions involving the large axial sulfur atom will tend to flatten that end of the cyclohexane ring attached to the two sulfur atoms. An examination of models of the two *s*-tetrathiane twist forms is revealing. Newman projections looking down the $H_2C–CS_2$ bond (eq 4) reveal the equatorial protons in the two *twist* forms (H_e in **7**; H'_e in **8**) to be nonequivalent because of proximate "up" or "down" S–S bonds. By use of the same rationale, the axial hydrogens H_a in **7** and H'_a in **8** are nonequivalent. Thus, the unique dynamical conditions which must prevail for **5** at −89° include slow cyclohexane ring reversal[13] and slow *s-tetrathiane twist-to-twist interconversion* (eq 4) on the dnmr time scale. In the event of rapid cyclohexane ring reversal and slow twist-to-twist interconversion, the CH_2 resonance would be averaged to a single AB spectrum as observed at −6°. In contrast, slow cyclohexane ring reversal and fast tetrathiane twist pseudorotation at −89° (eq 4) would time-average the resonances due to H_e and H'_e or H_a and H'_a giving a single AB spectrum which, of course, is not observed at −89°.



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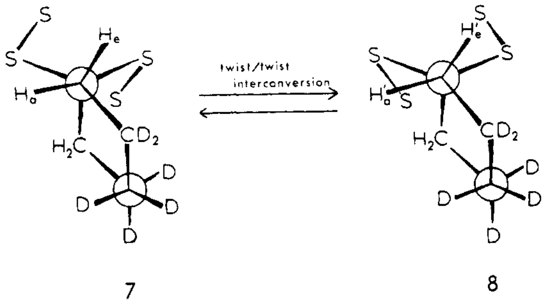


(4)

By the use of a locally modified version of computer program DNMR3[22] (see Experimental Section) and the dynamical model for **5** illustrated in eq 2, theoretical dnmr spectra were generated which gave good agreement with experiment. The essential features of the kinetic model for **5** are completely analogous to **4** and include: (1) no direct *s*-tetrathiane chair-to-chair or twist-to-twist conversion, (2) cyclohexane ring reversal barriers much lower than those for *s*-tetrathiane ring interconversion, and (3) no influence of one cyclohexane ring on the conformation, dynamics, or nmr parameters of the other. Using this model, one needs to specify eight molecular configurations with two nuclei in each, *i.e.*, to follow one CH_2 group in its travels through the dynamical itinerary of eq 2. Chemical shift assignments determined from a complete line-shape analysis at −89° and defined in accord with eq 2 are listed in Table III. In eq 2, the conversion of configuration **10** to **11** or **14** to **15** represents *cyclohexane* ring reversal on the *s*-tetrathiane twist and **9** to **16** or **12** to **13** the analogous process for the *s*-tetrathiane chair (eq 3). At temperatures above −70°, it was also assumed that rapid cyclohexane ring reversal will average differential $^1H–^2H$ spin-spin coupling to a single

Table III. Static Nmr Parameters for **5** at −89°

Conformation[a]	Chemical shifts, ppm	Conformation[a]	Chemical shifts, ppm
9	1.34, 3.53	**13**	1.75, 1.57
10	2.43, 1.81	**14**	2.16, 1.35
11	1.35, 2.16	**15**	1.81, 2.43
12	1.57, 1.75	**16**	3.53, 1.34

[a] See eq 2.

value, and this averaged coupling was introduced by using one effective T_2 value in all the theoretical spectra. The discrepancy between the theoretical and experimental spectra at −89°, *i.e.*, different widths at half-height for the low- and high-field components of the two AB spectra, results from differential ^1H–^2H spin–spin coupling introduced by slow cyclohexane ring reversal. Broadening of the low-field AB components is best rationalized as being due to a stronger coupling of the protons to adjacent deuterons. In cyclohexane systems, the coupling of two vicinal axial protons is large (~8–12 Hz), while the vicinal coupling of axial to equatorial or equatorial to equatorial protons is small (~3–4 Hz)[4] consistent with the established effect of dihedral angle on the coupling constant. In view of this, the broadened resonances of the low-field AB components of the twist form indicating stronger coupling to ^2H can be assigned to the axial protons of a given methylene group of the cyclohexane ring in **7** and **8**. In contrast to the situation in most cyclohexane derivatives where the resonance due to an axial proton generally appears upfield from the equatorial,[4a] a reversal of trend occurs in **7** or **8**.

A number of interesting observations come out of the complete dnmr line-shape analysis for **5**. Relevant to prior discussion, the total dnmr line-shape analysis of **5** at −6° (Figure 3) clearly reveals the twist resonance to be a closely spaced AB spectrum resulting from a time-averaging of the two AB spectra observed at −89° by rapid cyclohexane ring reversal. The observation of an AB spectrum for the twist form of **5** at −6° requires nonequivalent protons in a given CH_2 group and, consistent with the trends in **3** and **4**, also requires our assumed dynamical model for **5** incorporating barriers for direct twist-to-twist and chair-to-chair interconversion which are greater than that for the chair-to-twist process. Thus, activation parameters for *s*-tetrathiane ring reversal in **3**[21f] and **4** are very similar to those for the *s*-tetrathiane twist-to-chair process in **5** ($\Delta H^* = 17.3 \pm 1.0$ kcal/mol; $\Delta S^* = 3 \pm 6$ eu; $\Delta G^* = 16.3 \pm 0.4$ kcal/mol at 48°). From the complete dnmr line-shape analysis, it is interesting to note that cyclohexane ring reversal proceeds somewhat faster when the *s*-tetrathiane ring adopts the chair conformation ($\Delta G^* = 10.1 \pm 0.3$ kcal/mol at −53°; $\Delta H^* = 10.3 \pm 0.8$ kcal/mol; $\Delta S^* = 1 \pm 6$ eu) as compared with the twist ($\Delta G^* = 10.5 \pm 0.3$ kcal/mol at −53°; $\Delta H^* = 9.6 \pm 0.8$ kcal/mol; $\Delta S^* = -4 \pm 5$ eu).

Another rationalization for the observation of two AB patterns for the twist form of **5** under slow exchange conditions (−89°) involves the orientation of the cyclohexane rings with respect to one another. In one diastereomer, the two cyclohexane chairs are oriented in the same sense and in the opposite sense for the other diastereomer. In principle, these two diastereomers could give rise to two different AB patterns even in the event of fast twist pseudorotation. By use of this model, the relatively large chemical shifts between the different axial or equatorial protons would require a significant long-range diamagnetic anisotropic effect which we consider to be unlikely. It seems more reasonable that the chemical-shift differences result from the known substantial diamagnetic anisotropy of proximate sulfur–sulfur bonds.

The above dnmr data for **5** demonstrate that all three rate processes possible for a six ring (*i.e.*, chair to chair, chair to twist, and twist to twist) have been slowed on the dnmr time scale.

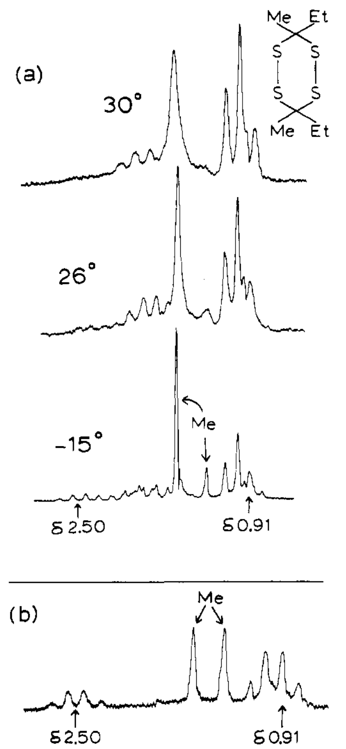
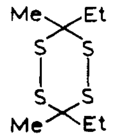


Figure 4. (a) The ^1H dnmr spectra (60 MHz) of 3,6-diethyl-3,6-dimethyl-*s*-tetrathiane (**17**) in CS_2. (b) The ^1H dnmr spectrum of the conformationally pure chair form of **17** in CS_2. (The spectra in parts a and b are on slightly different scales.)

Examination of the ^1H dnmr spectrum (60 MHz) of a presumed mixture of *cis*- and *trans*-3,6-diethyl-3,6-dimethyl-*s*-tetrathiane (**17**) in CS_2 revealed an exchange-broadened spectrum at 30° (Figure 4a). The spectrum sharpened at lower temperatures giving for the S_2CCH_3 group a large singlet (δ 1.56) and smaller singlet (δ 1.34) resonance. The large singlet peak (δ 1.56) is assigned to the twist conformer using a previous rationalization and the small singlet (δ 1.34) to the axial or equatorial S_2CCH_3 group of the chair conformer. Since methyl and ethyl have very similar conformational requirements, there should be a sister singlet of essentially the same intensity as that at δ 1.34, and it was apparent that this singlet was exactly superimposed on the large singlet peak (δ 1.56). Indeed, an experiment described below confirmed this analysis. The CH_2CH_3 groups gave a series of complex resonances with a dominant triplet (twist) superimposed on two smaller triplets (chair). The CH_2 resonances are quite complex, hinting again at nonequivalence in a given CH_2 of the twist form, *i.e.*, slow twist-to-twist interconversion.



17

Complete dissolution of crystalline **17** in CS_2 at −70° under conditions of very slow chair–twist stereomutation using a technique described previously for **3**[21bf] resulted in the dnmr spectrum in Figure 4b. The most salient features of this spectrum are two singlet resonances at δ 1.34 and 1.56 of equal area and two overlapping triplets (δ 1.04 and 0.91) of equal area giving an apparent 1:3:3:1 quartet. The most reasonable interpretation of this spectrum is a solution of the conformationally pure *chair* form of **17** with the two singlets and two triplets of equal area assigned to axial and equatorial methyl and ethyl groups, respectively. The quartet observed at δ 2.50 may be assigned to either an axial or equatorial CH_2 group of the chair with the other CH_2 resonance superimposed on and obscured by the other more intense upfield peaks. This observation is consistent with a preference for the chair conformer of **17** in the crystal and

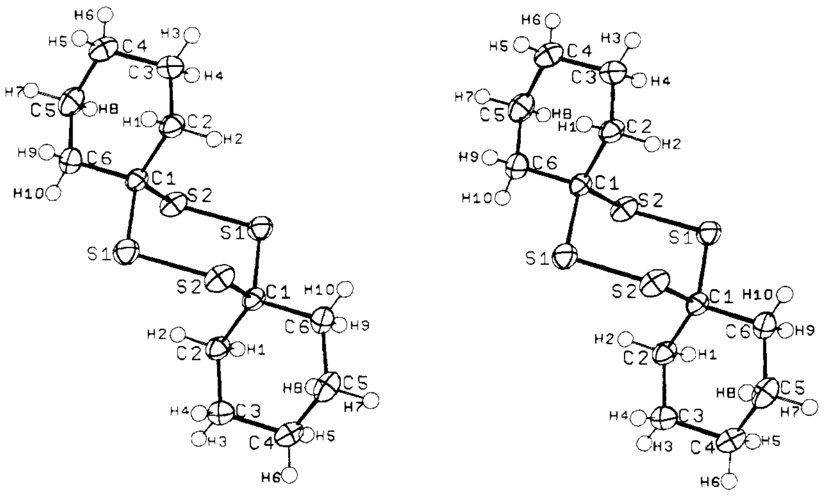


Figure 5. Stereoscopic view of the molecular structure of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane.

is in contrast to duplodithioacetone (**3**) which prefers the twist in the crystal as well as in solution.[21] The fact that **3** exists as the conformationally homogeneous twist in the crystal was deduced from solution nmr studies.[21bf] It is gratifying to note that a recently determined crystal structure of 3,3,6,6-tetramethyl-*s*-tetrathiane (**3**) revealed the molecule to be in the twist conformation,[25] in excellent agreement with our previous solution studies.[21b,f] It is interesting to note that the conformational preference of **17** is reversed in solution as compared with the crystal. When the sample of **17** was warmed from −70 to −15°, the system rapidly equilibrated to give a spectrum identical with that for **17** at −15° in Figure 4a.

The data presented here and previous results[21] enable the calculation of the *s*-tetrathiane chair:twist ratios in four *s*-tetrathiane derivatives (Table IV). The trends in conformational preference, especially the reversal associated with **4**, are generally consistent with our previous rationale that the chair:twist ratio is a function of both the *gem*-dialkyl effect and 1,3-sulfur lone-pair–lone-pair repulsions.[21d] Although it must be recognized that determination of $\Delta H°$ and $\Delta S°$ using the nmr method may be subject to systematic errors,[4a] measurement of K_{eq} (=[chair]/[twist]) as a function of temperature in the region of slow exchange on the dnmr time scale gave thermodynamic parameters for **3** ($\Delta H°$ = +0.2 ± 0.5 kcal/mol; $\Delta S°$ = −1.1 ± 0.5 eu) and **4** ($\Delta H°$ = −1.0 ± 0.5 kcal/mol; $\Delta S°$ = −2.0 ± 1.6 eu) indicating the *s*-tetrathiane twist to be a slightly more flexible species than the chair.

Table IV. The Chair–Twist Ratio in Various *s*-Tetrathianes at −15° in CS_2

Compd	K_{eq} = [chair]/[twist]	$\Delta G°$, kcal/mol
5	0.25	0.71 ± 0.05
3	0.43[a]	0.43 ± 0.05
17	0.56	0.30 ± 0.10
4	4.0[a]	−0.71 ± 0.05

[a] See ref 21d.

An X-ray crystallographic investigation of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane revealed that, in contrast to the solution conformational preference, the solid state has all three rings in *chair* conformations as shown in Figure 5. The crystals are triclinic, space group $P\bar{1}$, with unit cell dimensions a = 6.632 (6), b = 8.462 (6), c = 6.446 (6) Å; α = 93.92 (6), β = 103.23 (6), γ = 96.90 (6)°; and one molecule per unit cell, located at a center of symmetry. The density calculated from the X-ray data is 1.396 g cm^{-3}.

Table V. Atomic Coordinates in Crystals of 3,3:6,6-Bis(pentamethylene)-*s*-tetrathiane[a]

	X	Y	Z
S(1)	0.19282 (4)	0.11263 (3)	0.22060 (4)
S(2)	0.12329 (3)	0.17893 (3)	−0.08231 (4)
C(1)	0.1579 (1)	−0.1075 (1)	0.1854 (1)
C(2)	0.2956 (1)	−0.1710 (1)	0.0496 (1)
C(3)	0.2961 (2)	−0.3507 (1)	0.0513 (2)
C(4)	0.3574 (2)	−0.3978 (1)	0.2787 (2)
C(5)	0.2152 (2)	−0.3393 (1)	0.4132 (2)
C(6)	0.2132 (2)	−0.1589 (1)	0.4134 (1)
H(1)	0.450 (2)	−0.109 (2)	0.122 (2)
H(2)	0.250 (2)	−0.137 (2)	−0.106 (2)
H(3)	0.395 (2)	−0.386 (2)	−0.049 (2)
H(4)	0.148 (2)	−0.406 (1)	−0.025 (2)
H(5)	0.516 (2)	−0.342 (2)	0.350 (2)
H(6)	0.356 (2)	−0.521 (2)	0.276 (2)
H(7)	0.273 (2)	−0.366 (2)	0.572 (2)
H(8)	0.065 (2)	−0.400 (2)	0.355 (2)
H(9)	0.365 (2)	−0.107 (2)	0.483 (2)
H(10)	0.105 (2)	−0.125 (2)	0.500 (2)

[a] In this and the following tables, the standard deviation of the least significant digit is listed in parentheses.

Coordinates of the atoms are listed in Table V and thermal parameters in Tables VI and VII. Interatomic distances and angles are given in Tables VIII and IX. The model which was used in the calculations makes an allowance for polarization of the bonded hydrogen atom as described elsewhere.[26] With this model, the hydrogen coordinates more nearly represent the proton positions, and the C–H bond lengths are about 0.1 Å longer than if the more traditional method had been used.

The bond angles at C(1) deviate from regular tetrahedral in such a way that the molecule is more extended, and the cyclohexane rings are farther from the center than if these angles were tetrahedral. This bending of the molecule brings C(6) closer to sulfur than is C(2), and it is noteworthy that the C(1)–C(6) distance is longer than the other C–C bond lengths.

Experimental Section

The **60-MHz ^{1}H dnmr spectra** were obtained using a Varian HR-60A nmr spectrometer equipped with a custom-built variable-temperature probe.[27] The **100-MHz ^{1}H dnmr spectra** were obtained using a Varian HA-100 nmr spectrometer equipped with a Varian variable-temperature probe.

The theoretical ^{1}H dnmr spectra were calculated using a locally

Table VI. Anisotropic Thermal Parameters (Å^2)[a]

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
S(1)	2.556 (9)	2.338 (8)	2.670 (9)	0.389 (6)	−0.162 (6)	0.000 (6)
S(2)	1.828 (7)	2.680 (9)	3.26 (1)	0.213 (6)	0.542 (6)	0.924 (7)
C(1)	1.88 (2)	2.27 (3)	2.04 (3)	0.43 (2)	0.33 (2)	0.38 (2)
C(2)	2.24 (3)	2.90 (3)	2.51 (3)	0.89 (2)	0.85 (3)	0.71 (3)
C(3)	3.82 (4)	2.92 (4)	2.84 (4)	1.42 (3)	0.80 (3)	0.38 (3)
C(4)	4.52 (5)	2.97 (4)	3.36 (4)	1.60 (4)	0.46 (4)	0.90 (3)
C(5)	4.38 (5)	3.53 (4)	2.75 (4)	0.82 (4)	0.74 (3)	1.41 (3)
C(6)	3.28 (4)	3.33 (4)	2.05 (3)	0.97 (3)	0.48 (3)	0.55 (3)

[a] The form of temperature factor is $T = \exp[-0.25(B_{11}h^2a^{*2} + 2B_{12}hka^*b^* + \ldots)]$.

Table VII. Thermal Parameters for Hydrogen (Å)

	B		B
H(1)	3.4 (3)	H(6)	4.7 (3)
H(2)	3.4 (3)	H(7)	4.5 (3)
H(3)	4.4 (3)	H(8)	3.5 (3)
H(4)	2.8 (2)	H(9)	3.8 (3)
H(5)	3.9 (3)	H(10)	3.7 (3)

[a] The form of the temperature factor is $T = \exp(-B\lambda^{-2} \sin^2 \theta)$.

Table VIII. Interatomic Distances (Å)

S(1)–C(1)	1.841 (2)	C(2)–C(5)	2.941 (3)
S(1)–S(2)	2.035 (2)	C(2)–H(1)	1.08 (2)
S(1)–C(6)	2.688 (2)	C(2)–H(2)	1.05 (1)
S(1)–C(2)	2.796 (2)	C(3)–C(4)	1.523 (2)
S(1)–S(2)	2.980 (2)	C(3)–C(5)	2.509 (3)
S(1)–C(1)	3.072 (3)	C(3)–C(6)	2.944 (3)
S(1)–C(2)	3.419 (3)	C(3)–H(3)	1.07 (2)
S(2)–C(1)	1.842 (2)	C(3)–H(4)	1.03 (1)
S(2)–C(6)	2.692 (3)	C(4)–C(5)	1.521 (2)
S(2)–C(2)	2.827 (3)	C(4)–C(6)	2.522 (2)
S(2)–C(1)	3.071 (2)	C(4)–H(5)	1.08 (2)
S(2)–C(5)	3.220 (3)	C(4)–H(6)	1.04 (1)
S(2)–C(3)	3.328 (3)	C(5)–C(6)	1.528 (2)
S(2)–C(2)	3.393 (3)	C(5)–H(7)	1.06 (1)
C(1)–C(2)	1.519 (2)	C(5)–H(8)	1.04 (1)
C(1)–C(6)	1.537 (2)	C(6)–H(9)	1.03 (2)
C(1)–C(3)	2.528 (2)	C(6)–H(10)	1.06 (1)
C(1)–C(5)	2.543 (2)	H(1)–H(2)	1.72 (2)
C(1)–C(4)	2.961 (2)	H(3)–H(4)	1.67 (2)
C(2)–C(3)	1.521 (2)	H(5)–H(6)	1.71 (2)
C(2)–C(4)	2.516 (2)	H(7)–H(8)	1.71 (2)
C(2)–C(6)	2.525 (3)	H(9)–H(10)	1.74 (2)

Table IX. Bond Angles, deg

S(2)–S(1)–C(1)	104.7 (1)	C(2)–C(1)–C(6)	111.4 (1)
S(1)–S(2)–C(1)	104.7 (1)	C(1)–C(2)–C(3)	112.5 (1)
S(1)–C(1)–S(2)	108.0 (1)	C(2)–C(3)–C(4)	111.5 (1)
S(1)–C(1)–C(2)	112.3 (1)	C(3)–C(4)–C(5)	111.0 (1)
S(1)–C(1)–C(6)	105.1 (1)	C(4)–C(5)–C(6)	111.6 (1)
S(2)–C(1)–C(2)	114.2 (1)	C(5)–C(6)–C(1)	112.1 (1)
S(2)–C(1)–C(6)	105.3 (1)		

modified form of computer program DNMR3[22] (Program 165, Quantum Chemistry Program Exchange, Indiana University). The local modifications of DNMR3 include removing the subroutine ALLMAT for calculating eigenvalues and eigenvectors and adding CBABK2,[28] CBAL,[28] COMHES,[29] and COMLR2[30] which are a group of subroutines taken from the Eigensystems Subroutine Package (EISPAK) obtained from Argonne National Laboratories. The matrix inversion subroutine NVRT was replaced by a locally revised version of MATINC (ANL F4535) by B. S. Garbow of Argonne National Laboratories. The complex matrices were each separated into two real matrices representing the real and imaginary parts, respectively, and much of the computation was converted to real arithmetic except for complex multiplication and division. These modifications of DNMR3 provided significantly improved numerical stability and allowed the use of much larger rate constants and application to more complex spin systems. Using a DEC PDP-10 computer, the modifications decreased memory use by approximately 30%, and CPU time decreased by 60–70%. In addition, the coding in the original DNMR3 which automatically time averaged the dnmr spectrum if the rate constant were 1000 times the largest chemical shift difference was removed.

Dimethyl Succinate-2,2,3,3-d_4. Sixty-five grams (0.46 mol) of freshly distilled 2-butynedioic acid dimethyl ester (Aldrich Chemical Co., Inc.) was mixed with 0.3 g of platinum oxide (Matheson Coleman and Bell) and deuterated with deuterium (99.5%, Matheson Gas Products) in a Parr hydrogenation apparatus under a pressure of 40 psi of deuterium until the required amount of deuterium (0.92 mol) was absorbed. The solution was filtered and distilled at reduced pressure to give 62.0 g (89.1%) of dimethyl succinate-2,2,3,3-d_4: bp 79° (11 mm) [lit.[31] bp 80° (11 mm)]; nmr peaks (60 MHz, CCl_4) at δ 3.62 (6 H sharp singlet, methyl protons).

1,4-Butanediol-2,2,3,3-d_4. A solution of 60 g (0.40 mol) of dimethyl succinate-2,2,3,3-d_4 in 100 ml of anhydrous ether was added slowly to a stirred suspension of 25 g (0.66 equiv) of lithium aluminum hydride in 600 ml of anhydrous ether. The reaction mixture was allowed to reflux for 3 hr and cooled, and 125 ml of 10% sulfuric acid was added slowly with stirring. The aqueous phase was saturated with solid sodium chloride and continuously extracted with ether for 2 days to recover the diol. The ether was removed under vacuum and the residue distilled at reduced pressure to give 18.5 g (50%) of 1,4-butanediol-2,2,3,3-d_4: bp 119° (10 mm) [lit.[31] bp 120° (10 mm)]; nmr peaks (60 MHz, CD_3COCD_3) at δ 3.53 (4 H singlet, C-1 and C-4 protons) and 4.22 (2 H singlet, OH protons). The product had a retention time essentially identical with that of 1,4-butanediol on 20% SE-30 30–60 Chromosorb W (10 ft × 0.25 in.) column at 180° with a helium flow rate of 100 ml/min.

1,4-Dibromobutane-2,2,3,3-d_4. Dry hydrogen bromide gas (Matheson Coleman and Bell) was passed with stirring into 18.5 g (0.20 mol) of 1,4-butanediol-2,2,3,3-d_4 heated to 100°. The temperature was raised to 135°, and a slow current of HBr gas was passed for 6 hr. The crude bromide was separated from the aqueous layer, dissolved in ether, washed with 100 ml of water and three times with 100 ml of 10% sodium carbonate solution, dried (Na_2SO_4), and concentrated by vacuum distillation of the ether, and the residue was distilled at reduced pressure to give 36.1 g (82%) of 1,4-dibromobutane-2,2,3,3-d_4: bp 72–73° (10 mm) [lit.[32] bp 76° (11 mm)]. The product had identical retention time with 1,4-dibromobutane on 5% FFAP 60–80 Chromosorb W (5 ft × ⅜ in.) column at 180° with a helium flow rate of 100 ml/min. Nmr peaks (60 MHz, CCl_4) were at δ 3.37 (4 H singlet, C-1 and C-4 protons).

1,4-Butanedioic-2,2,3,3-d_4 **Acid.** 1,4-Dibromobutane-2,2,3,3-d_4 (36.1 g, 0.16 mol) in 75 ml of ethanol was added to a solution of 21.5 g (0.33 mol) of potassium cyanide in 25 ml of warm water. The mixture was refluxed for 12 hr with stirring and cooled, and the ethanol was removed under reduced pressure. The solid residue was extracted five times with 100-ml portions of dry, redistilled ethyl acetate and dried (Na_2SO_4), and the solvent was removed by vacuum distillation. The residue was distilled under reduced pressure to give 12.5 g (68.7%) of 1,4-butanedinitrile-2,2,3,3-d_4: bp 180° (20 mm) [lit.[32] bp 181° (20 mm)]. The dicyanide was refluxed for 9 hr with 250 g of sulfuric acid (50% by weight), cooled, filtered, and recrystallized four times with water to obtain 12.1 g (48.8%) of colorless crystals of 1,4-butanedioic-2,2,3,3-d_4 acid: mp 149–150° [lit.[32] mp 150°].

Cyclopentanone-*3,3,4,4-d*$_4$. 1,4-Butanedioic-*2,2,3,3-d*$_4$ acid (12 g, 0.08 mol) was mixed well with 1 g of finely powdered, crystalline barium hydroxide and heated to 285–295° gradually over a period of 1.5 hr in a sand bath. The temperature was maintained at 290° until most of the residue had distilled over. The ketone was separated from the water in the distillate, dried (anhydrous K_2CO_3), and distilled at atmospheric pressure to give 4.5 g (63.8%) of cyclopentanone-*3,3,4,4-d*$_4$: bp 129° (760 mm) [lit.[32] bp 130° (760 mm)]; nmr peaks (60 MHz, CCl_4) at δ 2.04 (4 H singlet, C-2 and C-5 protons).

3,3:6,6-Bis(tetramethylene-*d*$_4$)-*s*-tetrathiane (4). A 7.5-ml portion of 20% aqueous ammonium polysulfide solution (Matheson Coleman and Bell) was added dropwise to a stirred mixture of 4.5 g (0.05 mol) of cyclopentanone-*3,3,4,4-d*$_4$ and 25 ml of ethanol cooled to ~4°. The reaction mixture was maintained at this temperature with stirring for 1 hr after addition and then stored in a refrigerator for 1 week. The precipitate formed was filtered, washed three times with 250 ml of ethanol, and recrystallized from ethanol four times using Norit to give 0.4 g (5.5%) of colorless crystals of 3,3:6,6-bis(tetramethylene-*d*$_4$)-*s*-tetrathiane: mp 149–150° [lit.[33] mp 151.5–153°]; nmr peaks (60 MHz, CS_2) at δ 1.74 and 2.80 (8 H, two broadened singlet resonances).

Cyclohexanone-*3,3,4,4,5,5-d*$_6$ was prepared by the chromic acid oxidation of cyclohexanol-*d*$_{12}$ (Diaprep Inc.) in acetone and water to cyclohexanone. Any remaining α deuterons in the resulting cyclohexanone were completely substituted by hydrogens using five exchanges in 10% aqueous Na_2CO_3.

3,3:6,6-Bis(pentamethylene-*d*$_6$)-*s*-tetrathiane (5). A 14-ml portion of 20% aqueous ammonium polysulfide solution (Matheson Coleman and Bell) was added to 6 g (0.058 mol) of cyclohexanone-*3,3,4,4,5,5-d*$_6$. The mixture was stirred in a stoppered flask for 3 days, then allowed to stand for 5 days until no more yellow precipitate had formed. The precipitate was filtered, washed with ethanol several times until it was colorless, and recrystallized in ethanol four times using Norit to give 1.1 g (12.4%) of colorless crystals of 3,3:6,6-bis(pentamethylene-*d*$_6$)-*s*-tetrathiane: mp 129–130° [lit. mp[33] 130.5–131.5°]; 99.6% deuterium by mass spectral analysis (*m/e* 304.116); nmr peaks (100 MHz, CS_2) at δ 2.02 and 2.54 (8 H, two broadened resonances of unequal intensity). 3,3:6,6-Bis(pentamethylene)-*s*-tetrathiane was also prepared according to the above procedure to give the following elemental analysis.

Anal. Calcd for $C_{12}H_{20}S_4$: C, 49.27; H, 6.89; S, 43.84. Found: C, 49.18; H, 6.85; S, 44.02.

3,6-Diethyl-3,6-dimethyl-*s*-tetrathiane (17). An 80-ml portion of 20% aqueous ammonium polysulfide solution (Matheson Coleman and Bell) was added dropwise with stirring to a mixture of 50 ml (0.56 mol) of 2-butanone and 100 ml of ethanol cooled to ~4° in an ice–water bath. The reaction mixture was maintained at this temperature with stirring for 1 hr after addition and then stored in a refrigerator for 3 weeks. The precipitate that formed was filtered, washed several times with ethanol, and recrystallized from ethanol–water mixture four times with Norit to give 0.8 g (1.2%) of colorless crystals of 3,6-diethyl-3,6-dimethyl-*s*-tetrathiane: mp 55–56°; nmr peaks (60 MHz, CS_2) at δ 1.02 (3 H multiplet, protons of methyl in ethyl group), 1.60 (3 H singlet, methyl protons), and 1.8 (2 H complex multiplet, methylene protons).

Anal. Calcd for $C_8H_{16}S_4$: C, 39.96; H, 6.71; S, 53.34. Found: C, 39.84; H, 6.73; S, 53.19.

X-Ray Diffraction Technique. A colorless crystal of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane with dimensions 0.30 × 0.17 × 0.03 mm was glued to a glass fiber and used for measurement of diffraction intensities with a Picker FACS-I automatic diffractometer system. A θ-2θ scan technique was used with a scintillation counter, Mo Kα radiation (λ 0.70926 Å for Kα_1), a graphite monochromator (set at $2\theta = 11.80°$), and a scan rate of 1° min^{-1} for 2θ. The temperature was about 24°. Standard deviations were assigned on the basis of counting statistics combined with $0.03I$ for other errors. In the interval $2\theta < 75°$, measurements of 3675 independent reflections yielded 2715 for which the intensity exceeded 3σ. Those weaker than this were given zero weight in the refinement. No correction was made for absorption or for extinction. With $\mu = 6.3$ cm^{-1}, the extreme transmission factors differed by less than 10%, and the ratios of observed and calculated structure factors gave no evidence of extinction. We used the scattering factors for neutral sulfur and carbon of Doyle and Turner[34] with dispersion corrections of Cromer and Liberman.[35] For hydrogen, the values of Stewart, Davidson, and Simpson[36] for polarized hydrogen were used.

The structure was solved by statistical phasing and Fourier synthesis. It was refined by a full-matrix least-squares procedure. In the last cycle of refinement with isotropic thermal parameters for hydrogen and anisotropic ones for other atoms, no parameter shifted more then 0.005σ. For 2715 reflections, $R = \Sigma|\Delta F|/\Sigma|F_o| = 0.025$ (0.038 including 960 zero-weighted data), $R_2 = (\Sigma w(\Delta F)^2/\Sigma w F_o^2)^{1/2} = 0.034$. The standard deviation of an observation of unit weight was 1.46.

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Supplementary Material Available. A listing of observed structure factors, standard deviations, and ΔF will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (150 × 148 mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-65.

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Conformational Analysis of 2-Alkylcyclohexanone–Lanthanide Chelate Complexes

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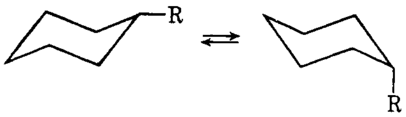
Abstract: The effect of added Eu(fod)$_3$ on the proton chemical shifts of 4-*tert*-butyl-, 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-*tert*-butylcyclohexanone has been analyzed to give the induced shift ratios for the two 5-position protons in the bound complex. Equations are derived for the use of induced shift ratios in conformational analysis and are used to obtain the conformational equilibrium constants for these substituted cyclohexanone-lanthanide chelate complexes. The factors responsible for the conformational preference of the 2-position alkyl groups are discussed.

Proton nmr spectroscopy has been a widely used tool for structural,[1] stereochemical,[1] and conformational analysis.[2] One critical limitation in the application of this tool is often insufficient chemical shift difference between protons in stereochemically different environments.[2] Hinckley's[3] observation that the dipyridine adduct of tris(dipivaloylmethanato)europium(III) caused large differential shifts in the proton nmr spectrum of molecules containing a Lewis base functionality held the promise of a way around this limitation. During the intervening years since Hinckley's observation, the efficiency,[4] understanding,[5] and application[5] of shift reagents has been greatly advanced by the many reports of the use of these reagents for structural,[6] stereochemical,[7] and conformational analysis.[8]

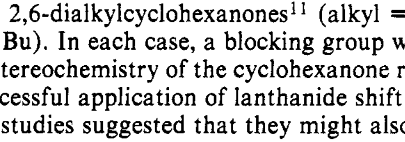
Nmr spectroscopy is particularly useful for conformational analysis of molecules in dynamic equilibrium.[2] A classic example is the chair–chair equilibrium of a substituted cyclohexane:



1 2

Proton nmr spectroscopy provides several methods for determining the mole fractions of **1** and **2** at equilibrium. The observed vicinal coupling constants for the equilibrium mixture are the mole fraction weighted averages of the characteristic coupling constants for each of the conformers. Similarly, the observed proton chemical shifts for the equilibrium mixture are the mole fraction weighted averages of the characteristic chemical shifts for the protons in each of the conformers. The choice of a suitable model compound from which characteristic chemical shifts and coupling constants can be obtained is a critical step in the application of this method. Regardless of which approach is used, sufficient spectral clarity is required so that coupling constant or chemical shift data may be readily and accurately obtained. An example in which this is not the case is provided by the nmr spectra of 2-alkylcyclohexanones.[9]

Although 2-alkylcyclohexanones (alkyl = Me, Et, *i*-Pr, and *t*-Bu) are known to undergo rapid ring inversion[2] (**3** ⇌ **4**), the complexity of the nmr spectra of these ketones precludes determination of the equilibrium constant by nmr spectroscopy. The conformational preference of a 2-alkyl group has been studied by base epimerization of the cis or trans isomers of either 2-alkyl-4-*tert*-butylcyclohexanones[10] or 2,6-dialkylcyclohexanones[11] (alkyl = Me, Et, *i*-Pr, and *t*-Bu). In each case, a blocking group was required to fix the stereochemistry of the cyclohexanone ring.



3 4

The successful application of lanthanide shift reagents to structural studies suggested that they might also be used to study problems involving dynamic equilibria. The ring inversion of 2-alkylcyclohexanones seemed to be a good problem on which to test this approach. The nmr spectra of the ketones are complex, the molecules contain the necessary basic functionality, there are only two isomers present at equilibrium, and the necessary model compound, 4-*tert*-butylcyclohexanone, is readily available.

Recently, we reported[12] preliminary results on the use of relative induced shifts to determine mole fractions of the axial and equatorial conformers of the 2-alkylcyclohexanones. We now report a more complete study of the 2-alkylcyclohexanone equilibria using lanthanide shift reagents. In the following paper, the application of lanthanide shift reagents to the determination of the rotational conformation of the 2-alkyl side chain of the cis and trans isomers of 2-ethyl- and 2-isopropyl-4-*tert*-butylcyclohexanone is reported.[13]

Results

The cyclohexanones used in this study were prepared by