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^{13}C NMR AND CONFORMATIONAL ANALYSIS OF SOME 1,4-DITHIEPANE SPIRANES

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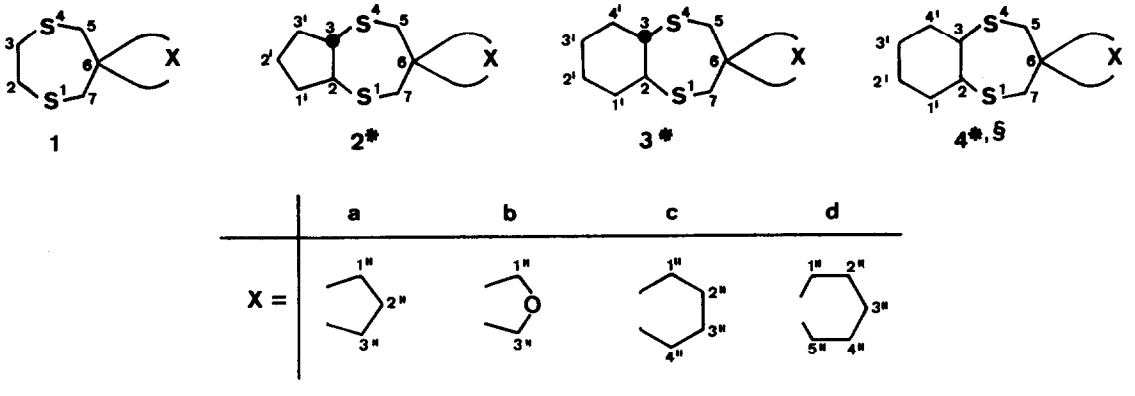
Abstract - The ^{13}C NMR spectra of four series of di- and tricyclic 1,4-dithiepane spiranes are presented. The cis-fused tricyclic derivatives **4a** - **4d** exhibit two coalescences in their 100.6 MHz spectra. These are discussed and assigned to conformational processes, namely a conversion of the molecules into their mirror images and a restricted pseudorotation of the dithiepane ring, respectively.

The chemistry of 1,4-dithiepanes has not been investigated in great detail. In this paper we want to report the ^{13}C NMR spectra of a number of bi- and tricyclic 1,4-dithiepane spiranes including investigations on their conformational behaviour. The syntheses of these compounds have been published earlier[1].



* The numbering in **2-4** does not correspond to the IUPAC-nomenclature for bicyclic molecules and has been chosen for sake of better comparibility.

§ The cis-fused tricyclic compounds **4** are racemates. The numbering of the atoms refers to the enantiomer shown above where the hydrogen atoms are α and S^1 is in axial position with respect to the cis-fused cyclohexane ring (cf. Fig. 3).

RESULTS AND DISCUSSION

The ^{13}C chemical shifts of the compounds **1a-1c**, **2a-2d**, **3a-3d** and **4a-4d** are listed in Table 1. The signal assignments were aided by "off-resonance" spectra, substituent-induced signal shifts, relative intensities and the consistency of the whole data body.

TABLE 1: ^{13}C chemical shifts of the 1,4-dithiepane spiranes **1a-1c**, **2a-2d**, **3a-3d** and **4a-4d**, recorded in $CDCl_3$ at 22.64 MHz and ca +30°C, relative to internal TMS

	C-2	C-3	C-5	C-6	C-7	C-1′	C-2′	C-3′	C-4′	C-1″	C-2″	C-3″	C-4″	C-5″
1a	38.4	38.4	44.5	45.9	44.5	--	--	--	--	32.7	14.2	32.7	--	--
1b	38.2	38.2	41.2	46.9	41.2	--	--	--	--	81.3	--	81.3	--	--
1c	38.6	38.6	44.6	51.1	44.6	--	--	--	--	38.6	24.9	24.9	38.6	--
2a	58.9	58.9	43.5	46.4	43.5	30.7	22.3	30.7	--	32.9	14.0	32.9	--	--
2b	59.3	59.3	40.7	47.4	40.7	30.7	22.4	30.7	--	82.0	--	82.0	--	--
2c	59.4	59.4	43.8	51.9	43.8	30.5	22.4	30.5	--	38.7	24.8	24.8	38.7	--
2d	59.1	59.1	42.6	41.3	42.6	30.5	22.4	30.5	--	36.0	21.8	26.1	21.8	36.0
3a	56.8	56.8	43.7	44.4	43.7	33.4	26.2	26.2	33.4	32.5	14.1	32.5	--	--
3b	57.2	57.2	40.8	45.8	40.8	33.4	26.1	26.1	33.4	81.6	--	81.6	--	--
3c	57.0	57.0	43.9	49.6	43.9	33.3	26.2	26.2	33.3	38.4	25.0	25.0	38.4	--
3d	56.6	56.6	42.5	39.1	42.5	33.3	26.3	26.3	33.3	36.0	21.9	26.2	21.9	36.0
4a	51.4	51.4	40.7	45.9	40.7	31.4	24.3	24.3	31.4	32.7	14.2	32.7	--	--
4b	51.5	51.5	37.7	47.0	37.7	31.2	24.1	24.1	31.2	81.6[a]	--	81.4[a]	--	--
4c	51.8	51.8	40.6	51.2	40.6	31.3	24.3	24.3	31.3	38.8[a]	24.9	24.9	38.2[a]	--
4d	50.8[b]	50.8[b]	38.9[b]	40.8	38.9[b]	31.1[b]	24.3[b]	24.3[b]	31.1[b]	36.2[a]	22.0	26.1	22.0	35.5[a]

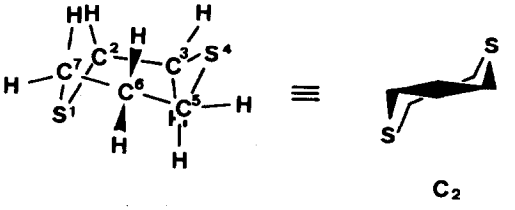
a May be interchanged.

b Signals are broadened due to coalescence effects.

Bicyclic 1,4-dithiepane spiranes 1a-1c

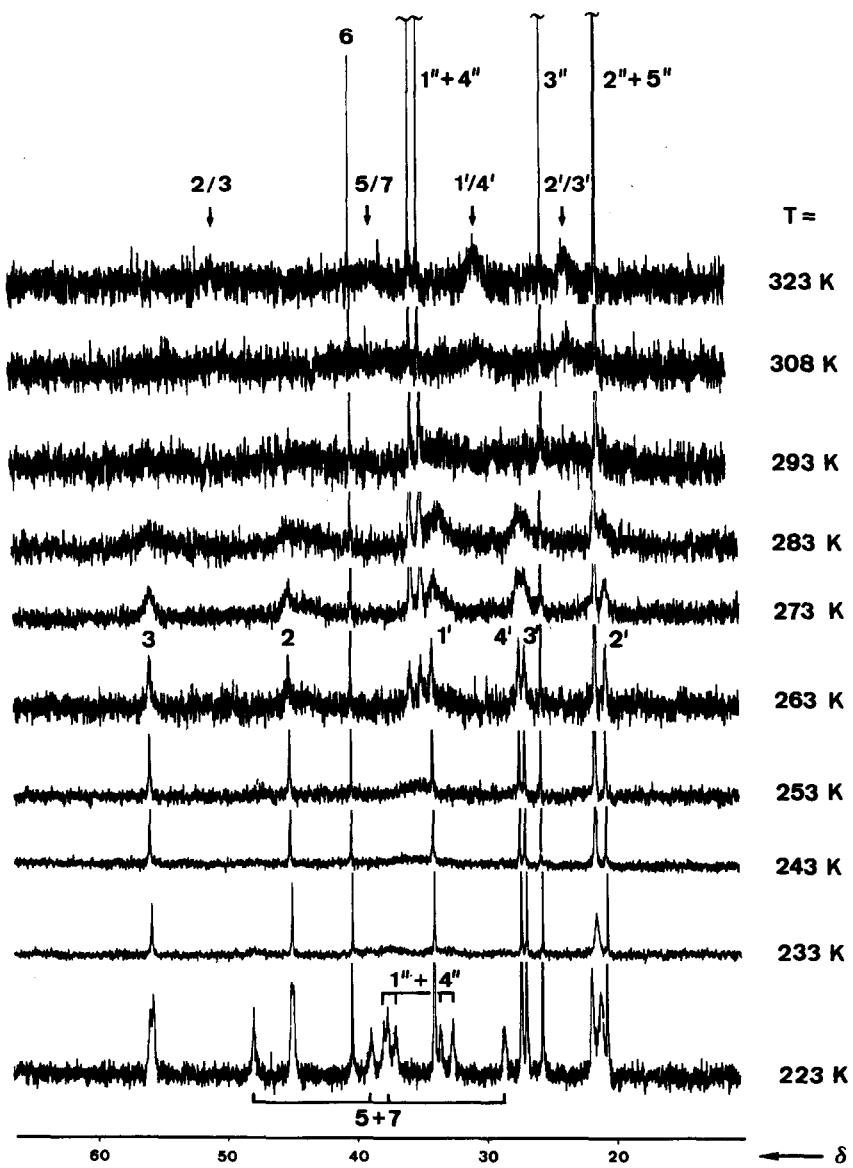
The assignment of the ^{13}C signals is straightforward except for the $C^{2/3}$ and $C^{5/7}$ pair. Here it relies on the following argument: When the methylene group C-2″ in **1a** is replaced by oxygen (**1b**) we observe an upfield shift of the $C^{5/7}$ signal (-3.4 ppm) because the γ effect of an endocyclic oxygen in such a stereochemical orientation is smaller than that of a methylene group[2]. A further confirmation for this assignment is the ^{13}C chemical shift of the $C^{2/3}$ signal (δ = 37.9) in 6-hydroxyl-1,4-dithiepane[3] which is very close to those in **1a-1c** (δ = 38.2-38.6). The conformational behaviour of seven-membered saturated rings is rather well established. Cycloheptanes[4] as well as 1,4-dithiepanes[5,6] have been found to prefer the twist-chair (TC) rather than the twist-boat (TB) conformation. In the heterocyclic case several TC forms are possible and it was reported[5,6] that the symmetrical TC form (Fig. 1) is the energetically most stable one.

Fig. 1: Symmetrical twist-chair (TC) conformation of 1,4-dithiepane



In 1,1-dimethylcycloheptane the TC pseudorotation barrier is assumed to be 5.5 kcal/mol and that of the TC-TB interconversion must be higher[4,7]. Moreover, the substituted carbon atom preferably adopts the isoclinal position[4,7]. Other authors reported that even at extremely low temperatures they were not able to freeze out any of the TC stereoisomers of cycloheptane[8]. From all this evidence we conclude that the preferred conformation of the bicyclic spiro-compounds **1a-1c** must be the symmetrical TC with a C_2-axis as represented by Fig. 1 with X replacing the two C^6 hydrogen atoms.

Fig. 2: Temperature-dependent 100.6 MHz ^{13}C NMR spectra of **4d** (in $CDCl_3$); for the numbering see footnote § of the formula scheme.



Trans-fused tricyclic 1,4-dithiepane spiranes 2a-2d and 3a-3d

For these compounds signal assignments are unambiguous. No safe statement on preferred conformations of the dithiepane rings can be made from the ^{13}C chemical shifts in this series. Models suggest that the symmetrical TC conformations should be favoured again whereas in the TB form H^2 and H^5 as well as H^3 and H^7, respectively, are rather near in space. Unfortunately, NOE experiments which might be able to exclude the TB form are not promising because the respective ^1H signals are too close to each other.

Cis-fused tricyclic 1,4-dithiepane spiranes 4a-4d

The compounds of the series **4** exhibit conformational motion effects in their ^{13}C NMR spectra. Fig. 2 shows the temperature-dependent spectra of **4d** at 100.6 MHz. Here we found two coalescence processes: The first at high temperature ($\sim 310 \pm 10$ K; $\Delta G^{\neq} = 13.7$ 0.2 kcal/mol) which involves signals of the seven- and the cis-fused six-membered ring leading to 1:1 splittings in the low-temperature region of this coalescence. On the other hand, the six signals of the spiro-ring (C^6, $C^{1''}$ - $C^{5''}$) are unaffected. At low temperature (243 ± 20 K; $\Delta G^{\neq} \approx 10$-12 kcal/mol) we observe a second coalescence of the signals of C^2, C^3, C^5, C^7, $C^{1''}$, $C^{2''}$, $C^{4''}$ and $C^{5''}$; it should be noted that C^5 and C^7 do not show two distinct peaks between both coalescence. The second process affords again splittings into two signals each of approximately equal intensity.

Assignment of the first coalescence in the spectra of **4d:**

Since the spiro-ring carbon atoms stay in identical positions and the others exchange their positions pairwise we conclude that the underlying conformational process interconverts the molecule into its mirror image. This is accomplished by an inversion of the cis-fused bicyclic system ($\Delta G_c^{\neq} = 13.7 \pm 0.2$ kcal/mol) similar to that of cis-decalin ($\Delta G_c^{\neq} = 12.6$ kcal/mol)[9].

The barriers of the analogues with smaller spiro-rings are somewhat lower: 12.3 ± 0.3 kcal/mol for **4a** and **4b** and 13.1 ± 0.2 kcal/mol for **4c**. In each instance four AX spin systems (C^2/C^3, C^5/C^7, $C^{1'}/C^{4'}$ and $C^{2'}/C^{3'}$) were evaluated using approximation equations for the reaction rates at the coalescence temperature[10].

Assignment of the second coalescence in the spectra of **4d:**

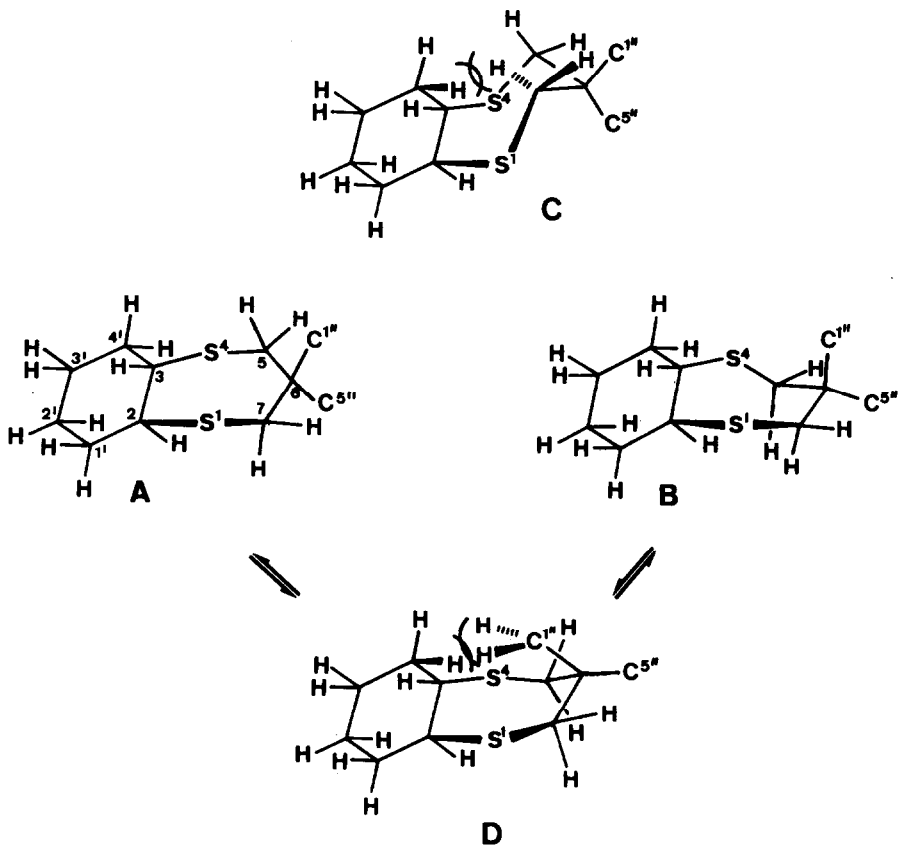
During the second process the signals of $C^{1''}$, $C^{2''}$, $C^{4''}$ and $C^{5''}$ split into two and the distance between those of $C^{1''}$ and $C^{4''}$ is approximately 5 ppm (1-2 ppm for $C^{2''}$ and $C^{5''}$). This is clearly too much to be explained by a slowing down of the spiro-cyclohexane ring inversion. In that case the conformers are diastereomers but the structural differences for the spiro-ring carbon atoms are rather small, since the diastereomers differ only in the fused cyclohexane annelation mode. Moreover, we found corresponding effects in the spectra of the other members of series **4** although their coalescences are at somewhat lower temperatures. This, however, is not at all consistent with the known energies in the conformation processes of four- and five-membered rings[11]. Thus, the underlying process must be an interconversion of two different, equally populated conformations of the dithiepane ring. An inspection of molecular models shows that the pseudorotation of this ring is restricted due to the annelation. In Fig. 3 some conceivable TC conformations within one enantiomeric series (cf. footnote § of the formula scheme) are depicted.

Structure **A** is a flexible TC with $C^{1''}$ and $C^{5''}$ being in rather similar positions. Structure **B** is a rigid TC with $C^{1''}$ and $C^{5''}$ in very different chemical environments since both sulfur atoms are in gauche orientation with respect to $C^{1''}$ but antiperiplanar to $C^{5''}$. Structure **C** must be of high energy due to a strong steric interference between the endo-hydrogen atoms at C^7 and $C^{4'}$ and can therefore be ruled out as a major contributor to the conformational process.

The **A** $\rightleftharpoons$ **B** interconversion is a pseudorotation and the question arises why its barrier (10-12 kcal/mol, estimated from the spectra) is so much higher than that in the monocyclic dithiepanes[5,6]. As models show the $C^{1''}$ and $C^{4'}$ methylene groups are very close to each other in the transition state **D** (Fig. 3) which has to be passed during the **A** $\rightleftharpoons$ **B** interconversion. This

steric compression can explain the extraordinarily high barrier. In addition, the potentially lower barriers[12] in **4a-4c** are understandable since here the bond angles $C^{1''} - C^{6} - C^{3''}$ and $C^{1''} - C^{6} - C^{4''}$, respectively, are smaller due to the reduced spiro-ring size and therefore the steric interference with the $C^{4'}$ methylene group is alleviated.

Fig. 3: Conceivable TC conformations of **4d** within one enantiomeric series (see footnote § of the formula scheme)



EXPERIMENTAL

The syntheses of the compounds **1-4** has been reported earlier[1]. The ^{13}C NMR spectra were recorded at ca +30°C in approximately 0.2 molar $CDCl_3$ solutions at 22.64 MHz using a Bruker WH-90 spectrometer. The temperature-dependent ^{13}C NMR measurements were carried out with ca 1 molar solutions at 100.6 MHz (Bruker AM-400). All chemical shifts are referenced to internal TMS.

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12 The lower coalescence temperatures in the spectra of **4a-4c** may also originate in smaller distances of the carbon signals involved in the low-temperature region. Since we measured in $CDCl_3$ solutions we cannot definitely decide whether this or a lower barrier is the reason.