A RIGID CONFORMATION FOR 5-FLUORO-2,11-DITHIA[3.3](1,4)NAPHTHALENOMETACYCLOPHANE WITH ABSENCE OF META-RING FLIPPING

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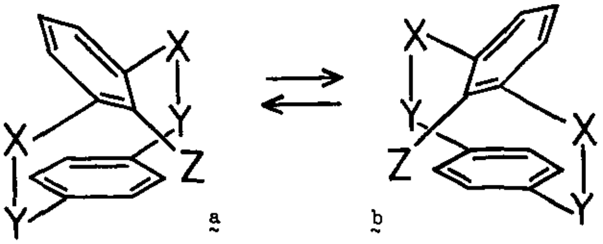
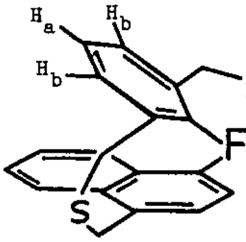
Abstract - ^{19}F and ^{1}H nmr data suggest the presence of only one major isomer for the title compound with the unexpected stacking of the benzene and naphthalene rings. Variable temperature ^{1}H nmr studies suggested no meta-ring flipping even at 160°C. The chemical shifts of the methylene protons were observed to be solvent and temperature dependent. This is attributed to the solvent effects on inversion processes of the bridges.

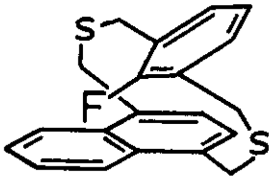
The pioneer investigations of [2.2]metaparacyclophane 1 by Cram[1] have indicated that the molecule undergoes conformatinal meta-ring flipping 1a ⇄ 1b. The energy barrier for the process was calculated to be 87 kJ mol^{-1}.[1] The conformational barrier in the corresponding dithiametaparacyclophane 2 was however not estimated presumably due a much higher conformational mobility.[2] Replacement of the intraannular proton with fluorine is known to increase significantly the conformational energy barrier in a number of cyclophanes.[3] Thus the fluoro-



	X—Y	Z
1	CH_2CH_2	H
2	CH_2SCH_2	H
3	CH_2SCH_2	F



4a



4b

substituted cyclophane 3 was found to exhibit a meta-ring flipping similar to 1a $\rightleftarrows$ 1b with a $\Delta G_c^{\ne}$ value of 76 kJ mol^{-1} with the coalescence temperature at 93°C.[2] We wish to report the synthesis and conformational study of the related 5-fluoro-2,11-dithia[3.3](1,4)naphthalenometacyclophane 4.

High dilution coupling of 1,4-bis(bromomethyl)naphthalene and 1-fluoro-2,6-bis-(mercapto-methyl)benzene gave the desired dithiacyclophane 4 in 31% yield. No other significant component was isolated from the chromatography of the reaction mixture. The general structure of 4 was clearly confirmed by a strong molecular ion at *m/z* 340 (86%) observed in the mass spectrum.

The chemical shift[2] for the fluorine in 3 appeared at -118.0 ppm (relative to $CFCl_3$). In the non-decoupled ^{19}F nmr spectrum of 4, an intense triplet centred at -117 ppm (relative to CF_3COOH and correlated to $CFCl_3$) was observed. It would thus appear that the isolated isomer was **4a**. Examination of the ^1H nmr spectrum of 4 further supported the existence of **4a** as the major conformer. The H_a,H_b-protons were observed as two separate sets of triplets at δ6.61 and δ6.03 respectively with an integral ratio of 2:1. The meta-ring protons of 3 were however reported[2] to appear as a multiplet at δ7.05. We believe that the significant spatial requirement of the fluorine in **4a** causes the meta-ring to tilt closer (toward parallel) to the naphthalene moiety. The H_a proton will be

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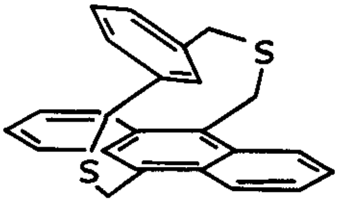
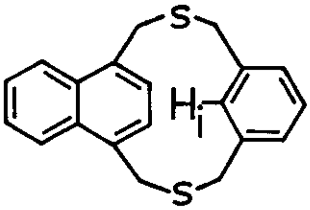
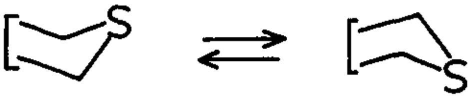




6

directly over the naphthalene ring and is thus deshielded significantly at δ6.03. The H_b protons however are slightly projecting outward and thus are not deshielded as effectively. A similar deshielding effect is also apparent when comparing the chemical shifts of the corresponding H_a,H_b-protons of 2 (δ7.2-6.8)[2] and 5 (δ6.6-6.2)[4]. This observation serves to support our above assignments. The two similar sets of methylene protons in dithiacyclophane 3 were observed as two overlapping AB quartets at δ3.71 (J = 13 Hz) and δ3.49 (J = 16 Hz) respectively.[2] By comparison the two significantly different AB quartets of 4a appeared at δ3.50 (J = 15.8 Hz) and δ4.19 (J = 13.2 Hz) should correspond to the respective benzylic (similar to those of 3) and naphthalylic methylene protons. We have thus shown that the major conformer of 4 obtained from the coupling reaction is indeed the isomer 4a.

Variable temperature (VT) ^1H nmr studies[2] of 3 have enabled the conformational energy for the meta-ring flipping to be estimated. It would thus be interesting to investigate the conformational behaviour of 4 similarly using VT ^1H nmr spectroscopy. This has in fact revealed another interesting observation. Various studies were made using $C_6D_5NO_2$, CD_2Cl_2, $CDCl_3$ and $C_6D_5CD_3$ as solvents. The respective signals of the aromatic protons remained practically unaltered in all cases. However, the δ_a-δ_b values of the two AB quartets changed significantly with temperature. The results summarised in Figure 1 clearly show that in all cases, the δ_a-δ_b changed linearly with temperature. The δ_a-δ_b values for both quartets increased with a temperature rise when the spectra were obtained in nitrobenzene, dichloromethane and chloroform. However, in toluene the δ_a-δ_b values of the higher-field quartet decreased with an increase in temperature. For the lower-field quartet, the changes in δ_a-δ_b are very different in the various solvents. For the higher-field quartet, the changes in dichloromethane, chloroform and nitrobenzene are similar but differ greatly from those in toluene. The above results obviously vary widely and give no consistent pattern to enable any generalization to be made. Knowing that there is no flipping of the meta-ring even at high temperatures (see below), the changes in δ_a-δ_b values described could be due to solvent effects on the nature of bridge



wobbling processes similar to those reported for some [3.3]cyclophanes.[5] The details of the effects would require further investigation.

The other interesting aspect to be investigated would be the possibility of the meta-ring flipping process **4a** $\rightleftarrows$ **4b** at high temperatures similar to that observed for 3.[2] The meta-ring protons in **4b** would not be as deshielded and would be expected to appear at lower field similar to that observed for 3 (ca. δ7.1). The two triplets assigned to the meta-ring protons of **4a** (δ 6.6, 6.0) would then be expected to shift if the flipping to **4b** occurs at higher temperatures.

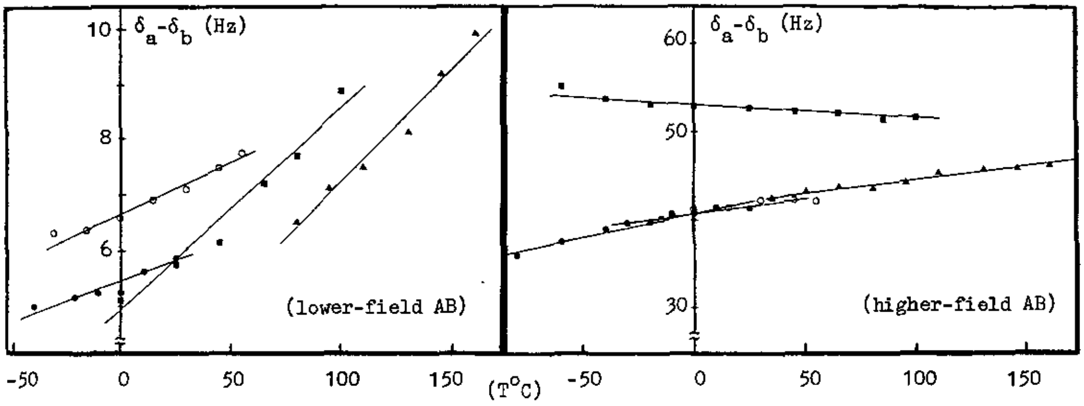


FIGURE 1. A plot of δ_a-δ_b vs temperature for dithiacyclophane 4 .

(●: CD_2Cl_2; ○: $CDCl_3$; ■: $C_6D_5CD_3$; ▲: $C_6D_5NO_2$)

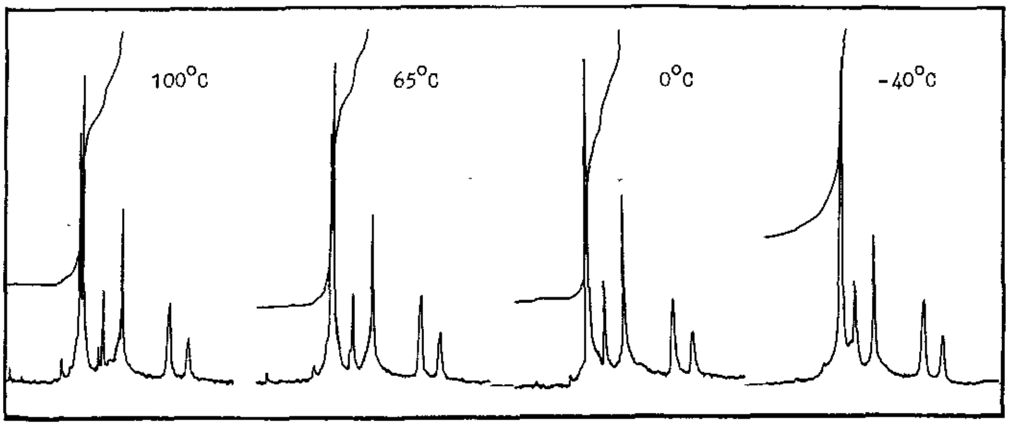
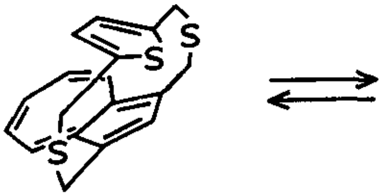


FIGURE 2. ^{1}H nmr spectra ($C_6D_5CD_3$; 90 MHz) of the methylene protons of dithiacyclophane 4 at selected temperatures.

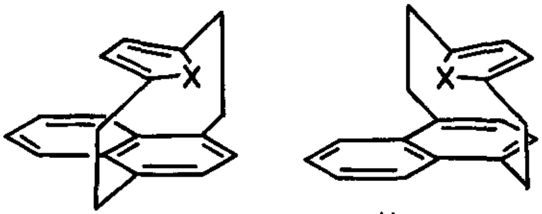
Averaged signals would be expected at equilibrium. However, both their chemical shifts and coupling constants remained practically unchanged from the ranges of 35 to 160°C (nitrobenzene) and -80 to 25°C (dichloromethane). The results seem to suggest that there is no flipping from **4a** to **4b** even at 160°C, although the same phenomenon can also be explained by assuming that the ratio of **4a** to **4b** stays constant during the change of the wide range of temperature. In the comformational studies[6] of the similar processes **7a** ⇄ **7b**, the methylene protons



7a

7b

were also observed as two sets of AB quartets at room temperature. These however coalesced at higher temperatures and eventually became sharp singlets. This coalescence phenomenon was clearly not observed for the two AB quartets of **4** (Figure 2) in the range of -60°C to 160°C as evident from the variable temperature studies described above. Simple line-shape consideration of the signal pattern of the methylene protons (Figure 2) does not seem to suggest any ring flipping process either. Perhaps more relevant information regarding the flipping process could be obtained from the conformational studies of the corresponding dithiacyclohane **6**. The 'internal' meta-ring proton H_i would serve as a more sensitive probe for nmr studies of the fluxional behavior. This is currently being investigated.



syn *anti*

8 , X = O, S, NH

The above result is in fact rather unexpected. The stacking of two parallel benzene rings in a cyclophane is, in principle, expected to be unfavorable due to the electronic repulsion. This point is reinforced in the conformational studies of heterophanes **8**.[7-9] The anti conformer was always the predominant or only isomer isolated. Our results however appear to suggest that the stacking of the benzene and naphthalene rings in syn **4a** could be favorably tolerated. This conformation with partially parallel rings is evident from the deshielding of the H_a proton as described. Presumably the steric interaction due to the close proximity of the fluorine atom over the naphthalene moiety or the dipole-interaction between the highly polarized C-F bond and the naphthalene π-cloud makes the anti **4b** much less stable.

ACKNOWLEDGEMENT

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