Registry No. **1b**, 113948-94-0; **1c**, 113948-95-1; **3**, 113948-96-2; **4**, 113975-13-6; **5**, 113948-97-3; **6**, 113975-14-7; **6** (acid chloride), 113949-06-7; **8**, 113948-98-4; **9**, 113948-99-5; **10**, 113949-00-1; **12a**, 113949-01-2; **12b**, 113949-02-3; **12c**, 113949-03-4; **14a**, 113949-04-5; **14b**, 113949-05-6; **15a**, 114029-37-7; ethyl 3-methyl-2,6-heptadienoate, 103273-76-3; 1-bromo-2-pentyne, 16400-32-1.

A Study of the Fluxional Behavior in 2,11-Dithia[3.3]orthocyclophane Using Molecular Mechanics and Dynamic NMR Analysis

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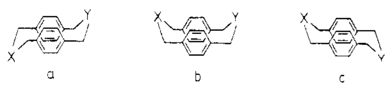
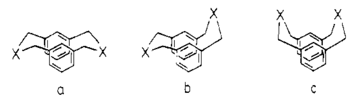
In the conformational studies of the fluxional behavior of [3.3]cyclophanes, a unique feature is the resemblance of their bridge-wobbling process to that in cyclohexane and derivatives. [3.3]Paracyclophane **1** was the first example of the series to be studied by variable-temperature ^{1}H NMR spectroscopy.[1] The results indicated that **1** exists as a mixture of the "chair" **1a** and "boat" **1b** conformations in a 1:2 ratio in solution. The free-energy conformational barrier was estimated[1] to be about 11.7 kcal mol^{-1}. Another independent study[2] of the same chair–boat interconversion also gave a similar energy barrier. A recent detailed structural study[3] of [3.3]metacyclophane **4** indicated that in the crystals, **4** exists as the conformer **4a**. Variable temperature NMR studies[3] also supported the existence of **4a** as the major isomer, with a barrier to isomerization to the other conformers of 11.5 kcal mol^{-1}. The conformational barriers for the $CH_2CH_2CH_2$ bridge inversion processes in **1** and **4** are thus very similar but found to be only slightly higher than that in cyclohexane (11.1 kcal mol^{-1}).[4] Conformational studies of the corresponding parent dithia[3.3]cyclophanes **2**[5] and **5**[6] were, however, less successful. In either case, the CH_2SCH_2 protons remained as an unresolved singlet even at very low temperatures. An obvious explanation would be due to the fast conformational interconversions with very low barriers; an alternative is the possibility that the two diastereotopic methylene protons in the "frozen" conformer have almost identical chemical shifts and are thus unresolved. The latter argument is supported by results from the conformational studies[7] of the thia[3.3]paracyclophane **3**. The energy barriers for the wobbling of the $CH_2CH_2CH_2$ (**3a** $\rightleftarrows$ **3b**) and CH_2SCH_2 (**3b** $\rightleftarrows$ **3c**) bridges were estimated at 11.5 and ca. 10 kcal mol^{-1}, respectively. The latter corresponds favorably with the conformational barrier in 1,4-dithiane (10.3 kcal mol^{-1}).[8] These data clearly show that although the longer CH_2SCH_2 bridge allows a higher flexibility, the conformational barrier for such a bridge inversion process may still be sufficiently high to be observed by ^{1}H NMR spectroscopy. Before this work, the fluxional behavior of the other parent dithia[3.3]cyclophane **6** was not examined. We now report the conformational studies of **6** by molecular mechanics calculations and variable-temperature ^{1}H NMR analysis.



1 : X = Y = CH_2 **2** : X = Y = S
3 : X = CH_2, Y = S



4 : X = CH_2 **5** : X = S

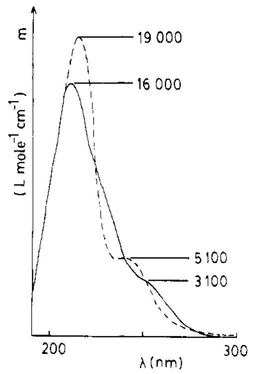
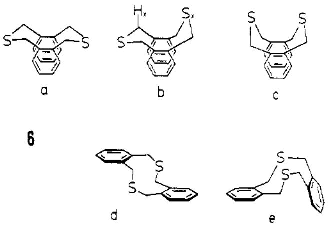


Figure 1. UV absorption spectra of **5** (—) and **6** (- - -) [30 mg/L in cyclohexane].



6

2,11-Dithia[3.3]orthocyclophane **6**[9] was prepared by the coupling of 1,2-bis(bromomethyl)benzene and 1,2-bis(mercaptomethyl)benzene under high dilution conditions. Our attempts using the reported procedure[10] gave much lower and nonreproducible yields of the desired product. In order to establish whether **6** is likely to adopt the syn conformation, the UV absorption spectrum of **6** (Figure 1) was compared to that of dithia[3.3]metacyclophane **5**, which is known to exist in the syn conformation in both solution (^{1}H NMR spectroscopy)[6b] and in solid state (X-ray crystallography).[6] UV absorption spectroscopy has been used in some cases to illustrate the face-to-face arrangement of two benzene rings in cyclophanes which normally result in bathochromic shift and broadening of absorption bands.[11,12] A significant difference between the spectra

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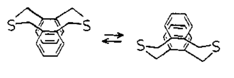
of **5** [λ_{max} 211 (ϵ 16 000), 253 nm (sh; ϵ 3100)] and **6** [λ_{max} 214 (ϵ 19 000), 241 nm (ϵ 5100)] taken in cyclohexane is the presence of a better resolved band at 241 nm in the latter compared with a shoulder band at 253 nm in the former. The close stacking of two parallel benzene rings in a cyclophane will be unfavorable due to electronic repulsion. In the dithiacyclophane **5**, the rings are held closely and practically parallel due to a more rigid meta-bridged system and result in a stronger interaction which causes severe band broadening and bathochromic shift. The ortho-bridged **6**, in order to minimize the electronic repulsion, will have the two benzene rings tilted further outward, which is made possible by the more flexible ortho bridges. This would reduce the interaction between the two aromatic π-clouds in **6** compared with **5**. The absorption bands of the former are thus expected to be less shifted bathochromically and better resolved. Although there is no significant change in the bands at ca. 210 nm of **5** and **6** (Figure 1), the latter does have a comparatively less bathochromically shifted and better resolved band at 241 nm. These results may thus suggest a syn conformation for the dithiacyclophane **6**.

In order to further support the preference for the syn conformation in **6**, MM2 calculations were performed to determine the energy difference between the most likely conformers. All the three syn conformers **6a–c** were considered. In the case of the anti conformation, the conformer, **6d**, in which the two benzene rings are parallel and that with nonparallel benzene rings, namely, **6e**, were included. Results from MM2 calculations do indicate that the syn conformer **6a** is the most stable, consistent with the finding of **4a** as the most stable conformer of [3.3]-metacyclophane.[3] Energies of the other conformers relative to **6a** are the following: *syn*-**6b**, 0.13 kcal mol^{-1}; *syn*-**6c** 7.71 kcal mol^{-1}; *anti*-**6d**, 1.11 kcal mol^{-1}; *anti*-**6e**, 4.55 kcal mol^{-1}. In conformer **6c**, a very large nonbonded interaction was observed between the sulfur atoms. As a result the 10-membered ring is twisted considerably to release the steric repulsion. The calculations showed that energies of **6c** and **6e** are very much higher, indicating that the population of these conformers would be negligibly small. On the other hand, the results suggest that the population ratio of **6a** to **6b** should be quite close to 1, with **6d** as a possibly observable minor conformer.

The results from the variable-temperature ^{1}H NMR studies of **6** are typical of a pair of diastereotopic protons giving rise to a coupled AB system.[13] A sample of **6** was examined by ^{1}H NMR spectroscopy at 90 MHz over the temperature range of 183–298 K. At 298 K, a simple spectrum of **6** was obtained with the methylene protons appearing as a singlet at δ 3.41. The aryl protons appeared as an expected AA′BB′ system with two sets of well-separated multiplets centered at ca. δ 7.2 and 7.5. A conformation of **6** with the rings tilting outward as suggested in the earlier discussion would be expected to result in marked difference in the magnetic environment of aryl H3 (H6) and H4 (H5) in **6**. Thus chemical shifts of the two types of aryl protons in **6** are appreciably different compared with the aryl protons in *o*-xylene which appear as a broad singlet.[14] As the temperature was lowered, changes appeared mainly in the aliphatic region of the ^{1}H NMR spectrum of **6**. The aromatic pattern remained practically unchanged with only little peak broadening, which could be due to a decrease in resolution as gradual precipitation of **6** was observed at the low-temperature limit. On the other hand, the singlet assigned to the methylene protons broadened and eventually began to show splitting at about 223 K. At still lower temperatures, the signal became a doublet and then completely resolved as a coupled AB quartet, indicating a slow rate of exchange among the conformers. Variable-temperature ^{13}C NMR studies, however, showed no significant broadening of the methylene carbon at 28.97 ppm even at 223 K.

In the conformational studies[7] of a series of [*m.n*]paracyclophanes related to **3**, it was found that rotation of the benzene rings involved much higher barriers than the conformational processes in the bridges. The results[3] from the study of **4** also indicated the absence of the flipping of benzene rings. On the basis of these results and the reported conformational behavior of the bridges in **1**, **3**, and **4**, dithiacyclophane **6** would be expected to exhibit a similar bridge wobbling process mainly between the two most stable conformers, **6a** $\rightleftarrows$ **6b**. However, in both the paracyclophane and metacyclophane systems, rotation or flipping of the benzene rings would involve much higher steric interaction between the aryl protons (C2/C3 ring protons in a paracyclophane and C2 ring proton in a metacyclophane) and the opposite benzene moiety as the rings try to get by each other. In **6**, the ortho-bridging system should allow more flexibility and easier flipping of the two benzene rings. Thus the conformational processes observed in the NMR studies of **6** could either be **6a** $\rightleftarrows$ **6b** or **6a** $\rightleftarrows$ **6a′**/**6b** $\rightleftarrows$ **6b′** (possibly via **6d**).



6a **6a′**

There are two sets of diastereotopic methylene protons in **6b**. In addition, results from our MM2 calculations indicated that the distance between H_x protons and sulfur S_x is short, and we can expect a large anisotropic shift to these protons. Thus at low temperature one can expect three AB quartets (one for **6a** and two for **6b**) when the conformational process **6a** $\rightleftarrows$ **6b** is frozen (**6a** and **6b** exist in about identical population). However, the DNMR results showed only one significantly sharp AB quartet. The likelihood of having accidental identical chemical shifts from three types of methylene protons in a mixture of two isomers having a 1:1 population distribution seems rather remote. Our DNMR results would then suggest that the dynamic process observed was in fact involving flipping of the benzene rings. The processes **6a** $\rightleftarrows$ **6a′**/**6b** $\rightleftarrows$ **6b′** could explain the temperature-dependent ^{1}H NMR spectra without any hypotheses. In the low-temperature limit, absence of ring flipping with continued wobbling of bridges would then account for the single averaged AB quartet observed. This is further support by the fact that both ^{13}C NMR signals and aromatic ^{1}H NMR signals showed no significant broadening. At the high-temperature limit, rates of interconversion of both the bridge-wobbling and ring-flipping processes are fast on the NMR time scale. The diastereotopic methylene protons become enantiotopic and thus isochronous, resulting in an averaged singlet.

In the ^{1}H NMR studies, taking the coalescence temperature (T_c) to be one at which no observable valley between the peaks in the AB system exists (225 K), the rate constant (k_c) of the observed conformational interconversion at T_c can be calculated by using eq 1.[13] The quantity $\Delta\nu$ is the maximum chemical shift difference of the two coupled protons at the low temperature limit where the rate of exchange is negligible (21.6 Hz), and J is the coupling constant of the AB system (14.7 Hz). The

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free energy of activation ($\Delta G_c^\ddagger$) at coalescence can then be estimated by using the Eyring equation (eq 2).[13] From

$$k_c = \pi/2^{1/2}(\Delta\nu^2 + 6J^2)^{1/2} \qquad (1)$$

$$\Delta G_c^\ddagger = 2.303RT_c(10.32 + \log T_c - \log k_c) \qquad (2)$$

the conformational studies of **6**, the value of $\Delta G_c^\ddagger$ at 225 K was calculated to be 11.0 kcal mol^{-1}. From the respective barriers of the $CH_2CH_2CH_2$ (11.5 kcal mol^{-1}) and CH_2SCH_2 (ca. 10 kcal mol^{-1}) bridge-wobbling processes of **3**, replacement of a CH_2 unit with sulfur seems to lower the barrier by ca. 1.5 kcal mol^{-1}. Introduction of two sulfur atoms such as in **2**, **5**, and **6** would be expected to decrease the conformational barrier to a greater extent. The $\Delta G_c^\ddagger$ value of 11.0 kcal mol^{-1} observed for the fluxional process in **6** would then seem too high for such a similar bridge-wobbling behavior. This serves as another indication that the barrier estimated in fact corresponds to the ring flipping process **6a** $\rightleftarrows$ **6a′**/**6b** $\rightleftarrows$ **6b′**.

The detailed study[3] of [3.3]metacyclophane **4** has provided evidence for the bridge-wobbling processes in a [*m.n*]cyclophane; our results on dithia[3.3]orthocyclophane **6**, however, strongly suggest that the observed conformational interconversion involves ring-flipping processes. In yet some other reported examples[15] of [3.3]cyclophanes, absence of ring flipping with wobbling of bridges could seemingly result in very similar chemical shifts (possibly unresolved) for the bridging methylene protons. The above results collectively suggest that DNMR analysis of [*m.n*]cyclophanes may not necessarily reveal an identical fluxional behavior. The observable process or processes would depend on the relative conformational barriers of bridge wobbling and ring flipping, both of which should differ from one [*m.n*]cyclophane to another and in turn depend significantly on the geometry of each cyclophane.

Experimental Section

^1H NMR spectra were determined on a JEOL FX90Q (90 MHz) Fourier transform spectrometer. ^{13}C NMR were recorded on a JEOL FX90Q Fourier transform spectrometer operating at 22.5 MHz. All chemical shifts are reported in ppm downfield from tetramethylsilane used as internal standard. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer. UV spectra were recorded on a Shimadzu UV240 Graphicord UV-vis spectrometer. Mass spectra were determined on a VG Micromass 7035 mass spectrometer at 70 eV with electron impact. Relative intensities are given in parentheses. Dithiametacyclophane **5** was prepared according to reported procedure.[16]

2,11-Dithia[3.3]orthocyclophane (6). A solution of 1,2-bis(bromomethyl)benzene (1.63 g, 6.2 mmol) and 1,2-bis(mercaptomethyl)benzene (1.05 g, 6.2 mmol) in degassed benzene (200 mL) was added dropwise using a rotaflow dropping funnel into a well-stirred solution of KOH (0.86 g, 15.5 mmol) in degassed 95% EtOH (500 mL) under N_2. After the addition, the mixture was stirred for 12 h at room temperature. The bulk of the solvent was then removed under reduced pressure. Dichloromethane and H_2O (1:1, 200 mL) were added, and the mixture was stirred until all solids dissolved. The organic layer was separated, washed with water, dried, and evaporated. The residue was chromatographed on silica gel with dichloromethane/*n*-hexane (1:1) as eluant to give **6**: 1.38 g (82%); mp 244-246 °C (lit.[10] mp 249-251 °C); ^1H NMR ($CDCl_3$) δ 7.63-7.49, 7.33-7.18 (m, AA′BB′, 8 H, Ar H), 3.41 (s, 8 H, CH_2S); IR (KBr) 1476, 1440, 1425, 1400, 1216, 1200, 1070, 1038, 945, 912, 825, 808, 765, 702, 664 cm^{-1}; UV (cyclohexane) λ_{max} 211 (ϵ 19000), 241 (5100) nm; MS, $M^{\cdot+}$ m/z (relative intensity) 272 (49), 135 (100), 104 (50), 91 (17); M_r calcd for $C_{16}H_{16}S_2$ 272.0693, found (MS) 272.0695.

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Registry No. 6, 7215-69-2.

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Structures of "Half-Opened" Cyclopropyl Cations. Theoretical Confirmation of Experimental Postulates

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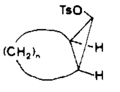
The parent cyclopropyl cation is not a minimum on the potential energy surface.[1] Hence, solvolysis of cyclopropyl derivatives normally leads to concerted disrotatory ring opening with the formation of allyl cation intermediates.[2-4] Woodward and Hoffmann's prediction that the orientation of the leaving group would determine the direction of this rotation, inward or outward,[4] has been verified inter alia by direct observation of the stereochemistry of product ions in superacid media.[5] This disrotational preference can lead to important differences in behavior, especially in bicyclo[*n*.1.0]alkyl systems **1** and **2**. The endo derivatives **1** solvolyze rapidly to give *cis,cis*-allyl cation intermediates **3** with relief of strain. However, as first postulated by Schöllkopf, Schleyer, et al.,[2] the exo derivatives **2** react to give only "partially opened" carbocation intermediates **4**. These arise because the required disrotatory



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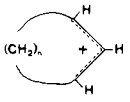

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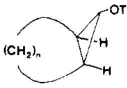

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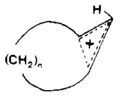

4

compd	rel rate[a]	compd	rel rate[a]
$c\text{-}C_3H_5OT_5$[b]	1	**2**, $n = 3$	10^{-4}[c]
1, $n = 3$	25 000	**2**, $n = 4$	1.7
1, $n = 4$	62	**2**, $n = 5$	2500
1, $n = 5$	3.1	**2**, $n = 6$	10 000
1, $n = 6$	3.5		

[a] Reference 2. [b] HOAc, 100 °C. [c] Reference 12.

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