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# Conformational Changes of 2,11-Dithia[3.3]metacyclophane. A New Look Using VT NMR and Calculation

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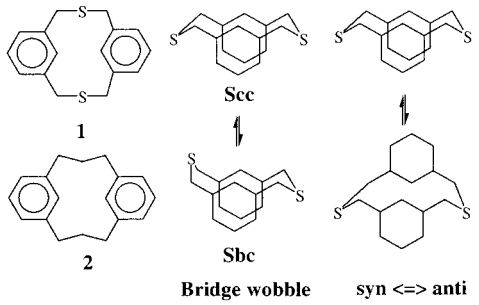
***Abstract:*** The conformational changes of 2,11-dithia[3.3]metacyclophane are reexamined utilizing VT NMR data and calculations (ab initio, semiempirical, density functional, and molecular mechanics) to show that the syn to syn′ inversion that occurs with exchange of the benzylic hydrogens proceeds most easily through bridge wobbles of the anti isomers and that the critical barrier is the conversion of the syn−chair−chair isomer to the anti−chair−chair isomer, barrier (found) = 9.3−9.6 kcal/mol, barrier (calc) = 10.3 kcal/mol, such that when this conversion is slow on the NMR time scale, the benzylic hydrogens no longer exchange, and the syn−chair−chair isomer becomes frozen. The syn−boat−chair isomer, however, can continue to invert to the anti−boat−chair isomer until lower temperatures, and thus, the benzylic hydrogens continue to exchange for this isomer. Thus, while bridge wobbles of the syn isomers have the largest barriers, bridge wobbles of the anti isomers have the smallest barriers, and so the barriers of the syn-to-anti conversions play a much greater role than previously determined.

## Introduction

Cyclophanes—bridged aromatic compounds—now pervade organic and organometallic chemistry as molecular properties has become the theme of the decade.[1] Understanding and being able to predict the shapes of cyclophanes is thus of some importance. Calculations, initially molecular mechanics, then semiempirical and now ab initio, have become so accessible that now even quite complex structures can be studied with desktop PCs. During this "calculation revolution", NMR has been a very valuable tool in analyzing cyclophane structure,[2] and this is even more so now that high-field spectrometers are much more common. Given the easy access by the novice to calculations, it is important to know just how well do they do. In this paper, we probe in fair detail the conformational processes of the simple, but fundamentally important cyclophane **1**. The molecule is a good model, because it is strained, has $\pi-\pi$ interactions, and has heteroatoms (with lone pairs) and a number of possible conformers.

In 1979,[3] we assigned the stereochemistry of **1** in the crystal state as the syn−chair−chair conformer, **Scc**, on the basis of its X-ray structure. Since, at that time, the $^1$H NMR spectrum at 90 MHz did not change with temperature, little could be said for sure about the conformational processes taking place. Because the benzylic protons appeared as a singlet, then the molecule either had not to be mobile and the two benzylic protons accidentally had the same chemical shift or *both* the syn ⇔ anti conversion *and* the bridge wobble was taking place, since only if both of these processes occur do the two protons fully exchange with each other. In 1985, Semmelhack[4] showed that [3.3]metacyclophane (**2**) also existed as the **Scc** conformer and was not able to detect any anti isomer in solution. In this case, however, the VT NMR spectrum was able to yield a conformational barrier of ∼11 kcal/mol, which they considered was consistent with a bridge wobble, i.e., **Scc** to **Sbc** (syn−boat−chair conformer). In 1988, Shinmyozu[5] stated that he believed that a syn ⇔ anti interconversion also took place. We had been reluctant to accept that the syn ⇔ anti interconversion




[Note: aromatic bonds omitted in conformers above for clarity]

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(1) Keehn, P. M.; Rosenfeld, S. M. *Org. Chem.* **1983**, *45*, 1−725, Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1−185, Vögtle, F. *Top. Curr. Chem.* **1983**, *115*, 1−159, Weber, E. *Top. Curr. Chem.* **1994**, *172*, 1−201, Bodwell, G. J. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 2085−2088, König, B. *Top. Curr. Chem.* **1998**, *196*, 91−136, Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, U.K., 1991.
(2) Mitchell, R. H. *Org. Chem.* **1983**, *45*, 239−310. Ernst, L. *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *37*, 47−190.
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(4) Semmelhack, M. F.; Harrison, J. J.; Young, D. C.; Gutierrez, A.; Rafii, S.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 7508−7514.
(5) Sako, K.; Hirakawa, T.; Fujimoto, N.; Shinmyozu, T.; Inazu, T.; Horimoto, H. *Tetrahedron. Lett.* **1988**, *29*, 6275−6278.


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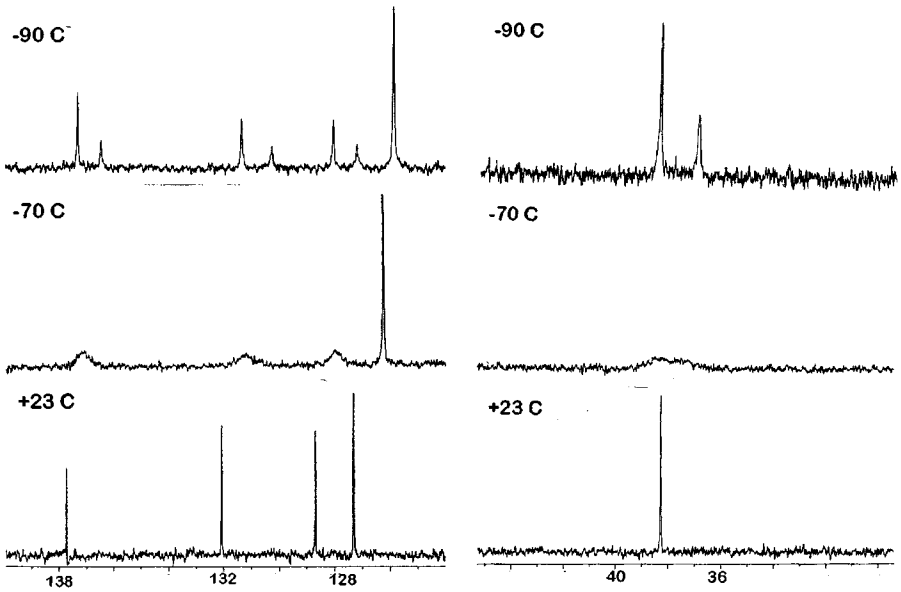



***Figure 1.*** Selected variable-temperature $^{13}C$ NMR spectra of **1** in $CD_2Cl_2$.

might be easier than the bridge wobble, but by 1988,[6] we also adopted the latter interpretation for the case of **1**. However, in this case, even though the 250-MHz spectrum was now available to us at −110 °C, experimentally the situation could not be resolved, since still no peaks changed. By that time, simple molecular mechanics calculations were possible, and these indicated that **Scc** was the lowest energy conformer, with the anti conformers 3−5 kcal/mol higher in energy. This was enough to indicate that these would not be present in any great amount in solution, but probably not impossible to pass through to invert the molecule. By 1992, Shinmyozu[7] obtained evidence to suggest that indeed the barrier for syn ⇔ anti interconversion was indeed less than that for the bridge wobble for **2**.

## Results

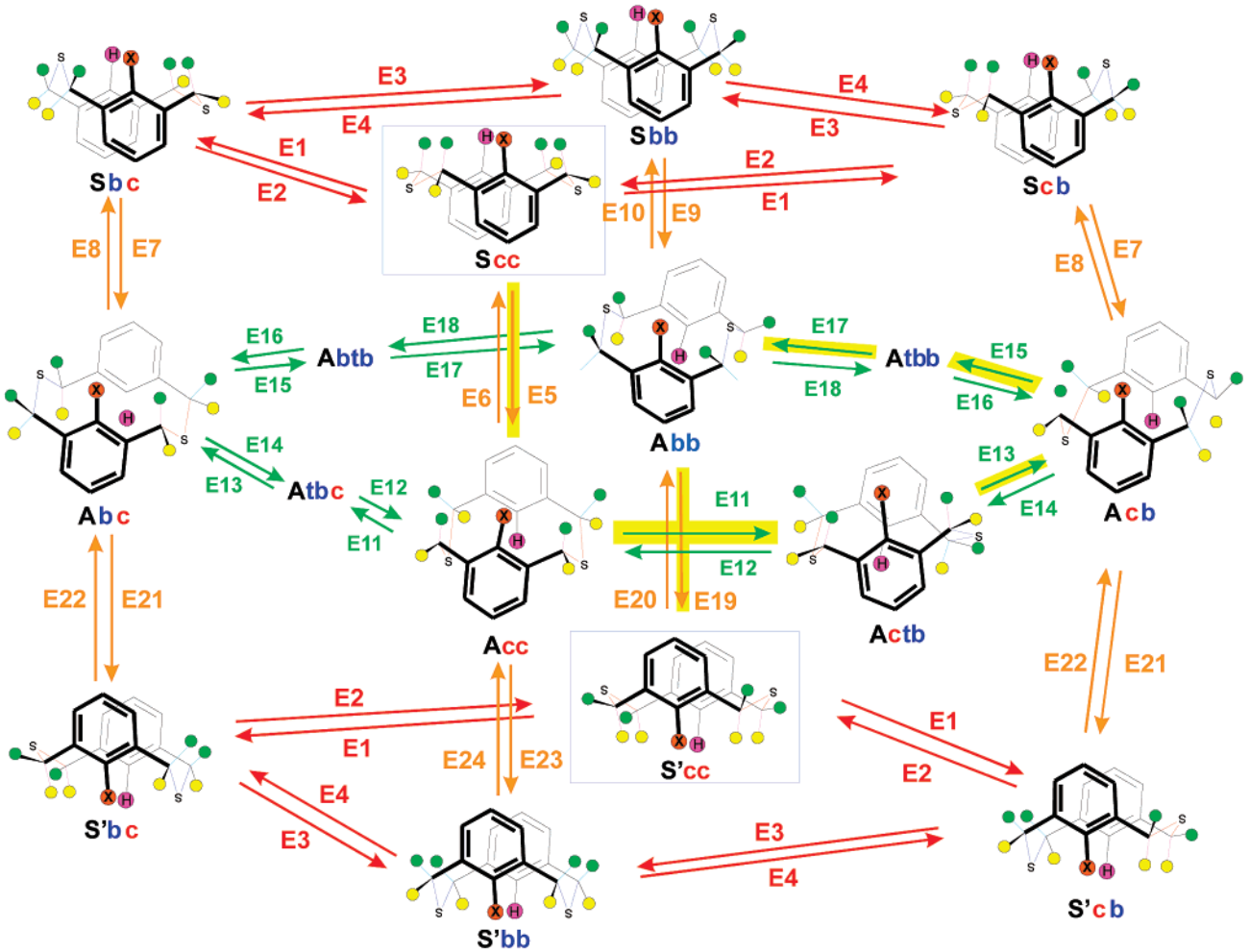
We have rerun the NMR spectra of **1** at higher field: 360 and 500 MHz for protons and 91 MHz for carbon. The carbon spectrum (Figure 1 and Supporting Information) is clearest: at ambient temperatures there are four aromatic and one alicyclic carbon lines. At −70 to −75 °C, these have all collapsed, and then on further cooling all but one aromatic line reappears as two lines in a 2:1 ratio. The low-temperature spectrum indicates two major conformers are present. From the −90 °C separation of the lines and a $T_c$ of 200 K, $\Delta G_c^{\ddagger} = 9.3-9.5$ kcal/mol.[2a] This is slightly less than the barrier for **2** above, as would be expected when a $-CH_2-$ is replaced by a −S−. The proton spectra (Supporting Information) are a little more informative. The benzylic proton singlet at $\delta$ 3.76 broadens on cooling and at −80 °C (360 MHz, −60 °C at 500 MHz) an AB pair of doublets begins to appear, which is clear at −85 °C (−65 °C, 500 MHz) together with a singlet. At −90 °C, the ratio of the two sets of peaks is 2:1, in agreement with the carbon data at this temperature. At −105 °C (∼−90 °C, 500 MHz), the singlet also begins to collapse while the AB remains sharp. Clearly, two conformers are present, in a 2:1 ratio, one of which is still able to exchange the benzylic hydrogens.

From the low-temperature spectrum and with a $T_c$ of 195K, $\Delta G_c^{\ddagger} = 9.6$ (±0.1) kcal/mol,[2a] in excellent agreement with the carbon result. The aromatic region is more complex. At +23 °C, the internal proton averages at $\delta$ 6.88, with the other protons at $\delta$ 6.90−6.97. However, as the temperature is lowered, the internal proton moves in among the others and, below −80 °C (−60 °C at 500 MHz), reemerges in part on the low-field side, reaching $\delta$ 7.10 at −105 °C. This clearly is still only consistent with a syn isomer, and the deshielding would be consistent with that expected from the −S− when the bridge is up, as shown in the **Sbc** conformer. At the same time, a less deshielded doublet (the aryl proton adjacent to the bridge) appears at $\delta$ 6.71 consistent with the −S− bridge being more distant on average. Because of the proton overlap, no clear $T_c$ can be seen, but it likewise appears to be around −80 °C. Further interpretation requires a more detailed look at the possible processes, and this follows.

**Conformational Processes.** The possible conformers for a mono substituted derivative of **1** and their interrelationships are shown in Scheme 1. In **1** itself, X = H, and the diagram is symmetric. The full diagram needs to be seen, however, since for the benzylic hydrogens to exchange (shown in green and yellow in Scheme 1), the **Scc** conformer must convert to the **S′cc** conformer (these are shown in blue boxes). There are a number of pathways by which this might occur. On the basis of our calculations below, and the NMR results above, we believe the most favorable route is that shown following the yellow arrows. To make this statement, estimates are required for each of the barriers to rotation, E1−E24, of Scheme 1. Fortunately, this is not as bad as it seems, in part because when X = H, there are several symmetric pairs, for example E5 = E20, which is not true when X is not equal to H (see below). As well, the barriers can be grouped into three types: (a) the bridge wobble of the syn conformers, which are shown in red and are all large, and so at low temperatures stop the direct interconversion of **Scc** with **Sbc**; (b) the bridge wobbles of the anti conformers, which are shown in green and are all too small to freeze out at temperatures that are accessible, and so proceed regardless; and (c) the *syn* ⇔ anti interconversions, which are

(6) Mitchell, R. H.; Weerawarna, K. S. *Tetrahedron. Lett.* **1988**, *29*, 5587−5588.
(7) Sako, K.; Shinmyozu, T.; Takemura, H.; Suenaga, M.; Inazu, T. *J. Org. Chem.* **1992**, *57*, 6536−6541.

*Scheme 1*




Note: chairs (with respect to the front ring) are shown having red -CH$_2$-S-CH$_2$- bonds, boats have blue. Axial bonds are in the plane of the benzene ring, and those parallel to the internal substituent are shown in magenta, those adjacent to the 5,7-ring H's are in cyan.

shown in orange, are intermediate in size, and are most important to this discussion, since at low temperature, it is essentially these that control whether the conversion **Scc** to **S′cc** occurs or not. To understand this point, for any of the syn conformers **S** to convert to the **S′** conformers (in order to exchange the benzylic hydrogens), an **S** to **A** conversion must occur. **Scc** can only directly convert to **Acc**, and if the latter flips the other ring to become **S′bb**, this now has to undergo a bridge wobble to reach **S′cc**. If **Acc** converts to **Abc** or **Acb** and then flips to **S′bc** or **S′cb**, a syn conformer bridge wobble still has to occur to reach **S′cc**. If **Acc** first does the bridge wobble to form **Abb**, and then converts to **S′cc**, the bridge wobble of the syn conformers is avoided. If E11−E18 are all small, and if E1−E4 are indeed all larger than E5−E10, then it is the latter barriers that control the exchange process in this case, since then **Acc** can easily convert to **Abb** to reach **S′cc**. So, even if the bridge wobble of the syn isomers is shut down, the **Scc**-to-**S′cc** exchange can still occur via bridge wobbles of the anti isomers. *This point seems not to have been stated succinctly previously.* How do we actually show this is the case for **1**? The $^{13}$C NMR spectrum of **1** sheds some light: conformer **Scc** should give a four-line spectrum in the aromatic region, but the only way that conformer **Sbc** can also give four lines is if the **Sbc** ⇔ Scb exchange is still occurring; however, at low temperature, the **Sbc** ⇔ **Scc** is shut down, and so the **Sbc** ⇔ **Sbc** exchange must be *through the anti isomers*. We do know that experimentally *no* anti isomer is frozen out at low temperature, because in an anti isomer the internal hydrogen is strongly shielded to $\delta \sim 5$.[8] Calculations must then at least support that two syn isomers are of lower energy than the anti isomers.

**Calculations.** The calculated relative stabilities ($H_f$) of the conformers of **1** using several methods are shown in Table 1. It should be noted that, in Scheme 1, for **1**, where X = H, then in energy **Sbc** = **Scb**, **Acc** = **Abb**, **Abc** = **Acb**, and **Abtb** = **Atbb** = **Actb** = **Atbc** (tb = twisted boat).

All methods find conformer **Scc** to be of lowest energy, and that **Scc** < **Sbc** < **Sbb**, and as well, all methods find conformer **Actb** to be lower in energy than the other anti conformers. In fact, the twisted boats are usually neglected, and it has mostly been stated[4,11] for [3.3]metacyclophanes that the anti conformers are 3−5 kcal/mol higher in energy than the syn conformer **Scc**. This is clearly probably not true for the twisted boat, **Actb**, which might play a larger role in the equilibrium than previously

(8) Vogtle, F.; Wieder, W.; Forster, H. *Tetrahedron. Lett.* **1974**, *15*, 4361−4364.
(9) PCMODEL v 5.13, Serena Software, Box 3076, Bloomington, IN 47402-3076.
(10) PC SPARTAN PRO v 1.07, Wavefunction Inc., Irvine, CA, 92612.
(11) Sako, K.; Tatemitsu, H.; Onaka, S.; Takemura, H.; Osada, S.; Wen, G.; Rudzinski, J. M.; Shinmyozu, T. *Liebigs Ann.* **1996**, 1645−1649. Fukazawa, Y.; Takeda, Y.; Usui, S.; Kodama, M. *J. Am. Chem. Soc.* **1988**, *110*, 7842−7847.

***Table 1.*** Comparison of Conformer Energies (kcal/mol) by Various Methods

| | PCM[a] | RHF[b] | MM94[c] | MM3[d] | AM1[e] | PM3[f] | DFT[g] | (DFT[h]) |
|---|---|---|---|---|---|---|---|---|
| **Scc** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Sbc** | 0.98 | 0.80 | 1.06 | 0.43 | 0.92 | 1.77 | 1.54 | 0.772 |
| **Sbb** | 1.73 | 2.48 | 3.11 | 1.03 | 2.40 | 3.57 | 2.23 | |
| **Actb** | 2.53 | 0.91 | 1.73 | 2.16 | 1.60 | 2.40 | 1.19 | 0.886 |
| **Acc** | 3.08 | 3.33 | 4.13 | 5.59 | 2.10 | 2.47 | 2.75 | |
| **Acb** | 4.80 | 4.17 | 5.41 | 6.13 | 2.12 | 3.97 | 3.50 | |

[a] PCMODEL[9] MMX = MM2 + $\pi$-SCF. [b]SPARTAN[10] Hartree−Fock 6-31G*. [c]SPARTAN[10] MMFF94 (an MM2 type); [d]PCMODEL[9] MM3. [e]SPARTAN[10]AM1. [f]SPARTAN[10] PM3. [g]SPARTAN pBP/DN** (pertubative Becke−Perdew with full polarization). [h]B3LYP (added at suggestion of reviewer; see text at end of discussion below).

***Table 2.*** Comparison of Conformer Populations (%) Based on Relative Energies in Table 1

| | PCM | RHF | MM94 | MM3 | AM1 | PM3 | DFT(pBP)[a] |
|---|---|---|---|---|---|---|---|
| | | | | At 300 K | | | |
| **Scc** | 68 | 51 | 69 | 45 | 60 | 86 | 82 |
| **Sbc** | 26 | 27 | 23 | 44 | 26 | 9 | 6 |
| **Sbb** | 4 | 1 | 0 | 8 | 1 | 0 | 1 |
| **Actb** | 2 | 22 | 8 | 2 | 8 | 3 | 9 |
| | | | | At 183 K | | | |
| **Scc** | 87 | 72 | 89 | 60 | 84 | 98 | 92 |
| **Sbc** | 12 | 16 | 10 | 36 | 13 | 2 | 2 |
| **Sbb** | 1 | 0 | 0 | 4 | 0 | 0 | 0 |
| **Actb** | 0 | 12 | 2 | 0 | 2 | 0 | 5 |

[a] Since only limited B3LYP data were available to us, the approximate ratios of **Scc**:**Sbc**:**Actb** at 300 K were 50:27:23 and at 183 K were 71:17:12.

thought. RHF, DFT, MM94, and AM1 predict a greater amount should be present at equilibrium than the other methods. The problem arises as to which calculation method is most reliable. Some handle on this can be obtained from the experimental results, at low temperature (183 K), the experimental ratio of isomers from the $^1$H NMR is 67:33 and from the $^{13}$C NMR is 68:32, and from the fact that at 300 K the amount of anti isomer on average present in the mixture is not much greater than 20%, because otherwise the internal protons $\delta$ 6.8 would be further upfield ($\delta_{anti} = \sim 5$; $\delta_{syn} = \sim 7$).[8] Table 2 shows the calculated populations at 183 and 300 K for the important conformers by the calculation methods used in Table 1.

At 183 K, only two isomers can be seen, **Scc** and an equilibrating **Sbc** ⇔ Actb ⇔ etc., in a 67:33 ratio, and thus in Table 2, the relevant comparison is % **Scc** and 100 − % **Scc**, and so the RHF method (72:28) and B3LYP (∼71:29) approximate this result best. MM3 underestimates the energy difference between the **Scc** conformer and the other conformers predicting a 60:40 ratio, while AM1, PCM (= PCMODEL), and MM94 overestimate (in that order) predicting 84−89:16−11 ratios; PM3 and Spartan pBP DFT considerably over estimate the energy difference. It is difficult to get a reliable estimate of the extent of anti isomers present at 300 K. Using the internal proton chemical shift (above) is only suggestive, because of the lack of a good anti conformer reference. For **1** (X = $NH_2$), the anti conformer is the one that exists in solution, and then the internal proton is at $\delta$ 5.0.[8] For **1** (X = $CH_3$),[12] the internal proton is at $\delta$ 5.5 (clearly mainly anti); however, projecting from that, the corresponding chemical shift when X = H has not enough precision to more than suggest that the contribution of the anti conformers at room temperature is about 10−20%. A reviewer regards the DFT methods of SPARTAN inferior to those obtained using a B3LYP calculation. Dr. Richard Williams (University of Idaho) kindly performed B3LYP calculations on **Scc**, **Sbc**, and **Actb** using Jaguar[13] to help resolve this difficulty, and these are included in Table 1. Clearly they are consistent with the RHF results, and together these two methods suggest that anti conformers play a significant role at room temperature, with ∼20% of anti isomers present.

**Barriers E1−E24.** Completely mapping the energy surface using RHF for a molecule the size of **1** was beyond our ability. However, using the dihedral drivers of both PCMODEL[9] and SPARTAN[10] to explore the conformational processes was possible for the molecular mechanics and semiempirical methods. The MMX force field in PCMODEL indicated that two bond rotations were critical. Basically, rotation about one of the C−S bonds controlled the bridge wobble and rotation about the Ar−C(bridge) bond the syn-to-anti inversion. By setting up a series of minimizations where both dihedral angles were driven over 1° steps, a map could be produced that indicated several pathways of converting one conformer to another were possible but that the lowest barriers were always obtained when the bonds above were rotated one at a time. In this way, the minimum energy barrier for conversion of each conformer could be estimated, and an estimate for each transition-state structure was obtained. Spartan also allows transition states to be generated; however, this appeared to be a real "hit and miss process" since only very occasionally was a state with one imaginary frequency obtained. However, the difference in energy from that found by the dihedral driving was minimal; for example, for the critical E5, Spartan yielded 6.78 kcal/mol (one imaginary frequency) using AM1, while dihedral driving yielded 6.81 kcal/mol, not a significant difference for use here. Dihedral driving worked well on all the barriers at the MM and semiempirical level. When this was completed, the energies of the transition-state structures were then explored using the ab initio RHF method, by making small dihedral changes, such that only a few ab initio calculations had to be done on each structure to find the energy maximum. From the energies of each transition state (available in the Supporting Information), the energies of each barrier in Scheme 1 could be estimated. The results of these calculations are shown in Table 3.

Although the actual numerical values vary somewhat between methods, it is interesting to note that all methods agree that the bridge wobbles of the syn conformers have high barriers, and specifically, barriers E1 and E2 (the wobbles to and from the Scc conformer) are higher than the barriers for conversion of syn to anti conformers, which are higher than those of the bridge wobbles of the anti conformers. All calculation methods support the idea that we presented above that the lowest energy path to achieve the **Scc**-to-**S′cc** conversion is for the **Scc** conformer to convert to the **Acc** conformer, and for this then to undergo bridge wobbles to the **Abb** conformer, and then for this to convert to the **S′cc** conformer (the yellow path in Scheme 1). As far as the NMR observations go, then the all important barrier in this conversion is E5 (E20), for **Scc** to **Acc**. As the temperature is lowered, this process becomes slow on the NMR time scale, and below $T_c$, the exchange of the benzylic hydrogens

(12) Boekelheide, V.; Tsai, C. H. *J. Org. Chem.* **1973**, *38*, 3931−3934.

(13) Jaguar v 4.0, Schrödinger, Inc., Portland, OR, 1991−2000.

***Table 3.*** Calculated Energy Barriers E1−E24 (kcal/mol) of Scheme 1[a]

| | method[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PCM | RHF | AM1 | PM3 | MM3 | MM94 | DFT*[c] | DFT**[d] |
| | | | | **S ⇔ S** | | | | |
| E1 | 12.6 | 12.1 | 7.1 | 7.3 | 10.3 | 18.8 | 12.9 | − |
| E2 | 11.6 | 11.3 | 6.2 | 5.6 | 9.9 | 17.7 | 11.2 | − |
| E3 | 12.4 | 9.9 | 7.0 | 7.0 | 10.2 | 18.3 | − | − |
| E4 | 11.6 | 8.2 | 5.5 | 5.5 | 9.6 | 16.2 | − | − |
| | | | | **S ⇔ A** | | | | |
| E5 (E20) | 10.4 | 10.3 | 6.8 | 7.2 | − | 16.3 | 8.9 | 8.4 |
| E6 (E19) | 7.3 | 7.0 | 4.7 | 4.7 | − | 12.1 | 5.7 | 6.0 |
| E7 (E22) | 6.6 | 6.0 | 3.9 | 3.4 | − | 10.9 | 5.1 | 3.1 |
| E8 (E21) | 2.8 | 2.6 | 2.7 | 1.2 | − | 6.5 | 2.5 | 0.6 |
| E9 (E24) | 5.9 | 3.6 | 3.1 | 2.2 | 8.7 | 8.9 | 2.8 | 2.9 |
| E10 (E23) | 4.6 | 2.8 | 3.4 | 3.3 | 7.7 | 7.8 | 2.2 | 2.7 |
| | | | | **A ⇔ A** | | | | |
| E11 (E18) | 2.0 | 1.0 | 0.2 | 0.2 | 0.4 | 1.8 | − | − |
| E12 (E17) | 2.5 | 3.4 | 0.7 | 0.9 | 3.8 | 4.2 | − | − |
| E13 (E16) | 3.6 | 4.4 | 1.2 | 1.6 | 4.2 | 4.9 | 4.8 | − |
| E14 (E15) | 1.4 | 1.1 | 0.6 | 0.1 | 0.3 | 1.2 | 2.4 | − |

[a] See footnotes in Table 1. [b] − indicates that the calculation was unstable and that the constraints would not hold. [c] *, DN* (numerical polarization). [d] **, DN** (full polarization).

stops. Even though **Sbc** could convert to **Abc** and then to **S′bc**, (smaller barriers), the latter could not reach **S′cc** because E2 > E5.

The observed barrier, at a $T_c$ of 195 K, $\Delta G_c^{\ddagger} = 9.6$ kcal/mol (9.3−9.5 kcal/mol from the $^{13}$C spectra), is in excellent agreement with the calculated values for E5 by RHF and PCM methods. AM1 and PM3 consistently underestimate all the barriers, while MM94 overestimates them. Clearly, PCMODEL (PCM) does a reasonably good job on the barriers, even though its calculated conformer energies relative to RHF were not as good. Certainly the conformational surface can be explored a lot more rapidly with PCMODEL than RHF, which may be rather important if larger molecules are studied!

Additionally, the exchanging benzylic hydrogens of the minor conformer **Sbc** still appear as a singlet at 195 K ($T_c$ for the **Scc** conformer), but which begins to collapse below 170 K. This is consistent with the calculated value for E7 of 6−7 kcal/mol.

Finally, when X is not equal to H in **1** (Scheme 1), inversion of the front ring containing X, e.g., **Abb** to **S′cc** or **Abc** to **S′bc**, should be prohibited at normal temperatures; i.e., the barriers E19−E22 all become very large, and thus, no syn ⇔ syn′ conversion can occur and the benzylic hydrogens can never exchange. Our results would suggest (assuming an X group does not affect the back ring inversion much) that still **Scc** to **Sbc** to **Sbb** could occur, probably through the anti conformers, and so freezing of this process at low temperatures on the NMR time scale should still be possible. Indeed, when X = Cl,[14] the benzylic hydrogens appear at room temperature as two sets of ABs, one widely spaced at $\delta$ 4.43 and 3.66 and the second narrowly spaced at $\delta$ 3.83 and 3.74 (this was not resolved in early NMR studies).[14] Since the benzylic protons are not a singlet, the **Scc**-to-**S′cc** conversion does not occur at room temperature. Note: when X = F, Vögtle[14] reported that the benzylic protons collapse to a singlet at ∼460 K, consistent with a much larger barrier for E19−E24. For X = Cl, on cooling the sample, both AB systems each collapse into two new ones, one of which continues to collapse as the temperature is lowered further, showing behavior very similar to the X = H case above. The $^{13}$C spectra also show behavior very similar to the X = H case: both of the two bridge carbons split in to two, and two of these collapse further at lower temperatures; all but one aromatic carbons split in to two signals as well. Clearly, this is consistent with the conformers **Scc** and **Sbc** being the low-temperature major isomers and that at low temperatures one *syn* ⇔ anti (presumably **Scc** to **Acc**) is shut down ahead of the other (**Sbc** to **Abc**). PCMODEL calculations give results similar to the X = H case above, except for E19−E24 and, for example, suggest that E1 = 12 kcal/mol, E5 = 10 kcal/mol, and E7 = 6 kcal/mol, leading us to very similar conformational processes as above. For X = Cl, using the $T_c$ method above, the barrier is estimated at 10.6 (±0.1) kcal/mol, in good agreement with the simple calculations. We will be reporting detailed results for a series of monosubstituted cases elsewhere in due course.

(14) Vögtle, F.; Schunder, L. *Chem. Ber.* **1969**, *102*, 2677−2683.

## Conclusions

The conformational inversion of 2,11-dithia[3.3]metacyclophane is not as simple as previously thought. The anti chair−twisted boat conformer, **Actb**, is considerably more stable than previously thought and plays a significant role in the conformational processes, such that the easiest pathway to interconvert the syn to syn′ isomers (**Scc** to **S′cc**, which exchanges the benzylic protons) is to avoid bridge wobbles of the syn isomers, i.e., go the path **Scc** to **Acc** to **Actb** to **Acb** to **Atbb** to **Abb** to **S′cc** in Scheme 1, rather than **Scc** to **Acc** to **S′bb** to **S′cb** to **S′cc** (or similar process).

Both PCMODEL and RHF 6-31G* calculations give good values (10.3 kcal/mol) for E5, the step that controls the observed NMR spectra, $\Delta G_c^{\ddagger} = 9.3-9.6$ kcal/mol (195 K). Conformational processes in related cyclophanes need now to be reexamined in light of these results.

## Experimental Section

The sample was prepared by us previously.[3] The NMR spectra were run on a Bruker AMX 360, at 360.14 MHz for protons and 90.6 MHz for $^{13}$C nuclei using $CD_2Cl_2$ as solvent. All spectra are available in the Supporting Information.

**Calculations.** The global conformational search engine of PCMODEL (GMMX) was first used to ensure that all conformers of **1**

had been found. The aryl−bridge carbon bonds and the bridge carbon−sulfur bonds were then rotated, separately, and then together, using the dihedral driver, to determine which rotations control which conformational changes; for example, starting from **Scc**, rotation about the aryl−bridge bond causes conversion in to **Acc**. Rotation steps were reduced to explore the transition state (top of barrier), with the rest of structure (except the driven dihedral angle) always minimized at each step. Driving two dihedrals produced maps, but these indicated that the lowest energy pathways were equivalent to driving one dihedral and minimizing the rest of the structure. In this way, an estimate for the energy of activation for each conformational barrier was obtained. Data for the other methods was obtained by using the PCMODEL-generated structures as inputs, such that a reduced dihedral range could be explored (especially for the RHF method), but data points either side of the energy maximum were always found. PCMODEL generated the MMX (MM2 + $\pi$ SCF) and MM3 data, SPARTAN generated the MMFF94, AM1, PM3, RHF 6-31G*, and pBP DFT data (see Table 1). The transition state for **Acc** to **Scc** was checked using SPARTAN's transition-state finder using AM1 (one imaginary frequency) and gave a value ($\Delta E < 0.03$ kcal/mol) almost identical to the value obtained above but was considerably more difficult to locate.

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**Supporting Information Available:** Tables of energies of the conformational transition states and absolute energy values for RHF and DFT calculations and VT $^{1}$H and $^{13}$C NMR spectra of **1** (X = H) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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