13-Methyl-2,6-dithia[7]metacyclophane: A Useful Molecule To Connect VT NMR Results and Structure with Calculations

Reginald H. Mitchell,[*,†] Rachel Blunden,[†] Gavin Hollett,[†] Subhajit Bandyopadhyay,[†]
Richard Vaughan Williams,[*,‡] and Brendan Twamley[‡]

Department of Chemistry, University of Victoria, P.O. Box 3065, Victoria, BC, Canada V8W 3V6, and
Department of Chemistry, University of Idaho, P.O. Box 442343, Moscow, Idaho 83844-2343

regmitch@uvic.ca

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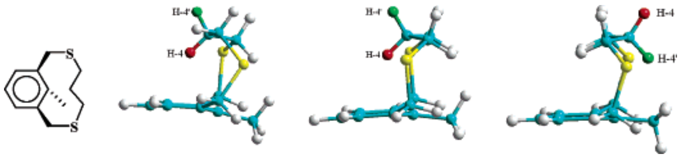
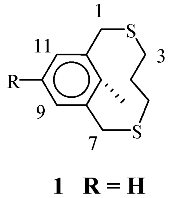


Ground state energies (DFT) and ^{1}H and ^{13}C NMR chemical shifts are calculated for the conformers of 13-methyl-2,6-dithia[7]metacyclophane (**1**), and the results are compared with X-ray structural data and variable-temperature NMR data, including the determination of the activation barrier. Calculations predict the correct low energy conformer with good agreement with chemical shifts, bond distances, and angles. VT NMR data for the 10-*tert*-butyl-substituted derivative **2** indicate that it undergoes the same conformational equilibria as **1**. This paper should enhance the confidence that organic chemists have in calculations to satisfactorily predict conformer energies.

Introduction

The difficulty of calculating the appropriate conformer(s) responsible for experimentally observed physical/chemical properties is well recognized. Even some manuals[1] warn that calculation of conformer energy differences is fraught with problems and that often the wrong ground state conformer is predicted. In this study, one of our aims was to establish the feasibility of identifying, using density functional theory (DFT), the conformers involved in the equilibria of 13-methyl-2,6-dithia[7]metacyclophane (**1**). We sought to, and believe we succeeded in, locating all energetically accessible conformers of **1** and in modeling their equilibria. The current interest in molecular properties has kept cyclophanes[2]—bridged aromatic compounds—as molecules of importance which now pervade organic and organometallic chemistry.[3] Understanding and being able to predict the shapes of cyclophanes is thus of great importance. We chose the relatively small molecule **1**, which although it has restricted conformational mobility has sufficient accessible conformers such that we can assess the performance of modern quantum mechanical calculations. We compare our calculated activation barrier, ^{1}H and ^{13}C NMR spectra, and structures with the corresponding experimental properties.



1 **R = H**
2 **R = *t*-Bu**

The internal methyl group of **1** keeps the cyclophane bridge from switching from one face of the aromatic ring

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[*] To whom correspondence should be addressed. (R.H.M.) Phone: 250-721-7159. Fax: 250-721-7147.

[†] University of Victoria.

[‡] University of Idaho.

(1) See, for example: Hehre, W. J.; Yu, J.; Klunzinger, P. E.; Lou, L. *A Brief Guide to Molecular Mechanics and Quantum Chemical Calculations*; Wavefunction, Inc.: Irvine, CA, 1998; p 70. Pettersson, I.; Liljefors, T. *Rev. Comput. Chem.* **1996**, *9*, 167.

(2) 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. Engl.* **1996**, *35*, 2085−2088. König, B. *Top. Curr. Chem.* **1998**, *196*, 91−136. Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, UK, 1991.

(3) See, for example: Abe, H.; Mawatari, Y.; Teraoka, H.; Fujimoto, K.; Inouye, M. *J. Org. Chem.* **2004**, *69*, 495−504. Baxter, P. N. W. *Chem. Eur. J.* **2003**, *9*, 5011−5022. Ludwig, R.; Dzung, N. T. K. *Sensors* **2002**, *2*, 397−416. Martinez, A. G.; Barcina. J. O.; Heras, M. D. C.; Cerezo, A. D.; Salvador, M. D. T. *Chem. Eur. J.* **2003**, *9*, 1157−1165. de Frutos, O.; Granier, T.; Gomez-Lor, B.; Jimenez-Barbero, J.; Monge, A.; Gutierrez-Puebla, E.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 2879−2890. Fedorova, O. A.; Gromov, S. P.; Alfimov, M. V. *Russ. Chem. Bull.* **2001**, *50*, 1970−1983. Yang, X. B.; Ding, S. T.; Yang, Y. S.; Zhou, X. H. *Chin. J. Org. Chem.* **2002**, *22*, 33−41.

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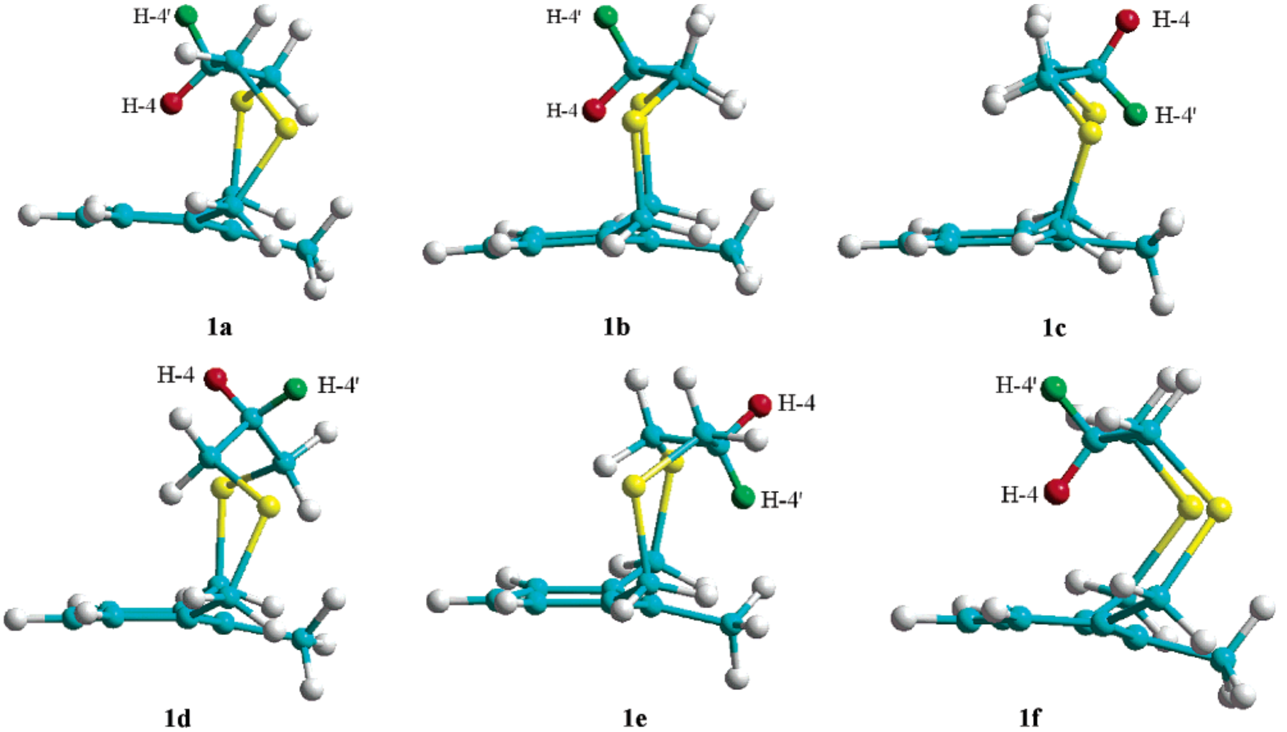

1a **1b** **1c**

1d **1e** **1f**

FIGURE 1. Six conformers found for **1**.

to the other, unlike the parent cyclophane which we studied in 1969,[4] while the length of the bridge limits the number of conformers and ensures reasonably distinct resonances in their NMR spectra. The corresponding 10-*tert*-butyl substituent of derivative **2** does not perturb the conformational processes but does simplify the NMR spectra by reducing the complex aromatic spin−spin couplings. These compounds are thus studied in this paper.

Results and Discussion

In 1970,[5] Vögtle first reported the synthesis of the thiacyclophane **1** from 2,6-bis-bromomethyltoluene and 1,3-bis-mercaptopropane. We used his method, and by substituting 2,6-bis(bromomethyl)-4-*tert*-butyltoluene, we also obtained the analogous phane **2**. Vögtle reported the 60 MHz ^{1}H NMR spectrum of **1** at that time, and on the basis that the AB for the benzylic protons did not collapse below 180 °C concluded that the bridge cannot swing from one face to the other face of the benzene ring. He did not comment on low-temperature processes. Although the bridge cannot switch from one aromatic face to the other, a certain amount of freedom is possible. After refinement of numerous contenders discovered by an extensive conformational search using PC MODEL,[6] Spartan,[7] and Hyperchem,[8] six conformers were located, with the lowest energy four being within about 2.5 kcal/mol of each other. These conformers are shown in Figure 1.

Note that conformers **1b**, **1c**, and **1f** are of C_s symmetry with the mirror plane passing through C10, C13, C14, and C4. In conformers **1a**, **1b**, and **1f**, the methylene proton **H-4** (shown in red in Figure 1) protrudes in to the π-cloud of the benzene ring and thus would be expected to be strongly shielded relative to **H-4′** (green), while in the other conformers this would not be true. Indeed, in the ^{1}H NMR spectrum of **1**, one proton appears highly shielded to δ −1.18 at ambient temperatures. At low temperature (175 K), the shielding increases, δ −1.79. The analogous proton **H-4′** appears at δ 1.18 and 1.06, respectively. Thus, at first glance, the two lowest energy conformers calculated (**1a** and **1b**) are consistent with the observed proton spectra. A more detailed comparison was thus embarked upon.

Structure Calculations

The various low-energy conformers found from a combination of PCMODEL[6] (MMX), Spartan[7] (AM1), and Hyperchem[8] (AM1) were refined to six conformers using the DFT B3LYP/6-31G* method as instituted in Gaussian 98.[9] We chose the B3LYP/6-31G* method for this study as we have previously shown that it provides excellent

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[4] Mitchell, R. H.; Boekelheide, V. *J. Heterocycl. Chem.* **1969**, *6*, 981−985.

[5] Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5299−5318.

[6] PCMODEL v 8.0, Serena Software, Box 3076, Bloomington, IN 47402-3076.

[7] Spartan 02 v 1.0.1, Wavefunction Inc., Irvine, CA, 92612.

[8] HyperChem 7.5, Hypercube Inc., Waterloo, Ontario, Canada.

[9] Gaussian 98, Revision A.9. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.

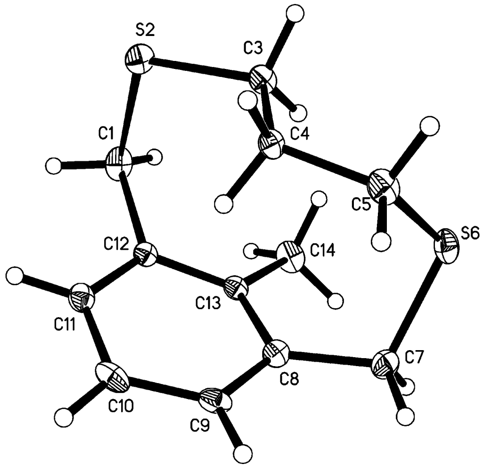

FIGURE 2. Thermal ellipsoid (50% probability) diagram of compound **1**.

TABLE 1. B3LYP/6-31G* Relative Energies (E_{REL}, Including Zero-Point Correction) for the Conformers 1a−f

conformer	E_{REL} (kcal/mol)	conformer	E_{REL} (kcal/mol)
1a	0	**1d**	1.753
1b	0.795	**1e**	4.954
1c	1.060	**1f**	8.451

TABLE 2. Comparison of Calculated (B3LYP/6-31G*) and Found (X-ray) Structures of 1a

	B3LYP/6-31G*	X-ray[a]	difference
bond length (Å)			
1−2	1.878	1.843(4)	0.035
2−3	1.852	1.825(3)	0.027
3−4	1.539	1.528(4)	0.011
4−5	1.546	1.537(5)	0.008
5−6	1.852	1.829(4)	0.024
6−7	1.870	1.825(4)	0.045
7−8	1.507	1.497(5)	0.010
8−9	1.398	1.381(5)	0.017
9−10	1.396	1.383(5)	0.013
10−11	1.390	1.385(5)	0.005
11−12	1.405	1.398(5)	0.007
12−1	1.506	1.504(5)	0.002
12−13	1.409	1.386(5)	0.023
13−14	1.516	1.521(5)	−0.005
dihedral angle (deg)			
9−8−13−14	−167.4	−169.3	1.9
11−12−13−14	167.0	168.8	−1.8
10−9−8−13	−3.6	−2.5	−1.1
8−9−10−11	−6.9	−7.3	0.4
9−10−11−12	6.5	6.8	−0.3
10−11−12−13	4.6	3.6	1.0
11−12−13−8	−14.8	−13.5	−1.3
9−8−13−12	14.4	12.9	1.5

[a] Crystallographic esd's were not used in determining the differences.

TABLE 3. Calculated Boltzmann Populations of Conformers 1a−f at 300 and 175 K

conformer	300 K	175 K	conformer	300 K	175 K
1a	67.3	86.5	**1d**	3.6	0.6
1b	17.8	8.8	**1e**	<0.1	0
1c	11.4	4.1	**1f**	0	0

modeling of a variety of aromatic systems[10] (the relative energies of these conformers using lower level methods are given in the Supporting Information section). Analytical energy second derivatives were calculated at all optimized structures to confirm that these are minima. The relative energies of each of these conformers are shown in Table 1, and the structures are illustrated in Figure 1.

The lowest energy conformer (**1a**) is thus not one of the symmetrical conformers (**1b**, **1c**, **1f**), but one where both sulfur atoms are different from each other. This makes every carbon and every hydrogen in the molecule different, and indeed, this is the structure found for the crystal using X-ray diffraction.

Crystal Structure Determination. The structure of **1** was solved and refined as orthorhombic, *Pbca*. A diagram of **1** is shown in Figure 2. Further technical details of the structural determination are provided in the Experimental Section and Supporting Information.

The most noticeable feature of the cyclophane is the nonplanarity of the phenyl system with a fold axis along C14, C13, and C10. There is a 13.9° bend between both halves of this system (as described by the planes C14 C13 C8 C9 C10 and C14 C13 C12 C11 C10). This is an uncommon feature among phenyl systems with calixarenes among the noticeable exceptions, e.g., 25,26,27,28,29-pentahydroxycalix(5)arene bis(acetone) clathrate[11] and (μ^2-calix(4)arene bis(crown-6))aqua(perrhenato)dicesium perrhenate sesquihydrate,[12] which have aromatic bending of ca. 7.2° and 8.7°, respectively. As can be seen from Table 2, the agreement between the calculated and observed data for **1a** is very good and supports our use of the B3LYP/6-31G* method to model this thiacyclophane. The calculated coordinates for **1a** and **2** were translated into crystallographic fractional coordinates (see Tables S6 and S7 in the Supporting Information), and the phenyl core (C8−C14) moiety was compared for all three systems. Using the OFIT subroutine in the program XP,[13] the superposition of this phenyl core for the X-ray model and the calculated conformers **1a** and **2** have a weighted rms (root mean square) deviation of 0.0153 and 0.0107 Å which shows how close a fit to experimental results the calculated models are. A superposition of **1a** and **2** using the same routine displays a weighted rms deviation of 0.0175 Å; hence, both calculated models are also very similar.

NMR Spectra

At ambient temperatures, the bridge is fluxional, and based on a Boltzmann population (Table 3, calculated using our B3LYP energies and assuming all species are singly degenerate and ignoring any entropy differences), all conformers may be accessible, though **1a**−**d** will

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[10] Williams, R. V.; Armantrout, J. R.; Twamley, B.; Mitchell, R. H.; Ward, T. R.; Bandyopadhyay, S. *J. Am. Chem. Soc.* **2002**, *124*, 13495−13505. Kimball, D. B.; Haley, M. M.; Mitchell, R. H.; Ward, T. R.; Bandyopadhyay, S.; Williams, R. V.; Armantrout, J. R. *J. Org. Chem.* **2002**, *67*, 8798−8811. Boydston, A. J.; Haley, M. M.; Williams, R. V.; Armantrout, J. R. *J. Org. Chem.* **2002**, *67*, 8812−8819.

[11] Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1133−1138.

[12] Thuery, P.; Nierlich, M.; Asfari, Z.; Vicens, J.; Dozol, J.-F. *Polyhedron* **2000**, *19*, 1749−1756.

[13] XP, interactive molecular graphics package, SHELXTL, v. 6.12, Bruker AXS Inc., Madison, WI, 2001.

TABLE 4. Experimental (175 K) and Calculated (1a−f) Chemical Shifts (δ) for the Protons H-4 and H-4′ and Carbons 1,7 and 3,5 of 1 and Differences (Δ) between Experimental and Calculated Values or Differences (Δ') between Experimental or Calculated Values for Analogous Atom Pairs (ppm)

no.	175 K	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
H-4	−1.79	−1.92	−0.87	1.61	1.13	1.47	−2.08
$\Delta(\mathrm{EXP}_{175\mathrm{K}} - \mathrm{CALC}_{\mathbf{1x}})$		0.13	−0.92	−3.40	2.92	−3.26	0.29
H-4′	1.06	0.71	1.25	0.86	1.00	1.28	0.47
$\Delta(\mathrm{EXP}_{175\mathrm{K}} - \mathrm{CALC}_{\mathbf{1x}})$		0.35	−0.19	0.20	0.06	−0.22	0.59
Δ'(4′-4)	2.85	2.63	2.12	−0.75	−0.13	−0.19	2.55
C-1	34.08	40.63	41.99	40.86	41.88	41.31	44.42
C-7	35.86	42.61	41.99	40.92	42.41	39.42	44.42
Δ'(7−1)	1.78	1.98	0.00	0.06	0.53	−1.89	0.00
C-3	25.56	32.47	38.68	34.54	32.09	31.82	36.81
C-5	30.04	36.45	38.68	34.52	30.32	37.54	36.81
Δ'(5−3)	4.48	3.98	0.00	−0.02	−1.77	5.72	0.00

predominate, while at temperatures ~175 K, the individual conformers are "frozen out" and the calculated difference in energy between the conformers is such that **1a** is predicted to predominate. Indeed at 175 K, a single conformer does predominate (see below), which shows unique proton and carbon resonances for each proton and carbon in the molecule. This immediately rules out conformers **1b**,**c**,**f** as the dominant low-temperature conformer, since they are of C_s symmetry, where, for example, H-1 and H-7 and similarly C-3 and C-5 would have identical NMR resonances, but does not rule out **1d** or **1e** or, of course, **1a**. To further verify that the low-temperature solution conformer is indeed **1a**, we calculated the proton and carbon shifts for each conformer to compare them to the experimental values. We have previously shown for a wide range of aromatics that the GIAO-HF/6-31G*//B3LYP/6-31G* method for ^{1}H shifts and Forsyth's[14] procedure to scale the GIAO-B3LYP/6-31G*//B3LYP/6-31G* ^{13}C absolute shieldings provide chemical shifts in excellent agreement with experiment.[10] We used these methods to calculate ^{1}H (the difference between the GIAO-HF/6-31G*//B3LYP/6-31G* absolute shieldings for the proton of interest and that for TMS) and ^{13}C chemical shifts for **1a**−**f** and report the results of these calculations along with the slow exchange limit chemical shifts at 175 K for **1** in the Supporting Information Table S1, with selected data being presented here in Table 4.

Pronounced agreement between experimental and calculated chemical shifts is considered to be good evidence that the calculated geometry is close to the experimental structure. As already noted, the symmetry of conformers **1b**,**c**,**f** eliminate them from consideration for the dominant low-temperature structure of **1**. Comparison of the observed NMR data with that calculated for **1a**, **1d**, and **1e** then leaves no doubt that **1a** is also the low-temperature solution conformer. The most significant result is for H-4, which is strongly shielded at δ −1.79. As Table 4 shows, only the calculated result for **1a** (δ −1.92) is consistent; those for **1d** and **1e** are completely different, with the H-4/(4′) proton shifts calculated to be 1.13 (1.00) and 1.47 (1.28), respectively. Likewise, the difference (Δ') between H-4 and H-4′, which experimentally is 2.85 ppm, agrees well with the calculated value of 2.63 ppm for **1a**, but not with the values calculated for **1d** or **1e**, 0.13 and 0.19 ppm, respectively. Other significant data which confirm the assignment as **1a** rather than **1d** or **1e** are from Table 4 Δ'(C5−C3) and Δ'(C7−C1), and from Table S1 (Supporting Information) Δ'(C12−C8), Δ'(H5−H5′), and Δ'(C11−C9). The chemical shifts calculated for **1a** are in good agreement with the proton (average deviation = 0.34 ppm) and carbon (average deviation = 2.7 ppm, excluding those next to sulfur) resonances observed for **1** at 175 K. Since the empirical Forsyth scaling was parametrized using compounds containing only C, H, O, and N, the calculated shifts for the carbons adjacent to sulfur (C-1,3,5,7) are in somewhat poorer agreement (average deviation = 6.7 ppm) with the corresponding experimental shifts. When the data is taken collectively, assignment of the structure for the dominant low-temperature species to conformer **1a** is reasonably certain.

Variable-Temperature (VT) NMR Spectra. The measurement of VT NMR spectra has enabled many cyclophane conformational processes to be elucidated.[15] Both VT proton and carbon data were obtained for **1**, and the relevant partial proton spectra are shown in Figure 3 (full spectra are available in the Supporting Information).

Since **1b** is symmetrical, either sulfur atom can move to give **1a** or its enantiomer **1a′**, which results in a high-temperature exchange (**1a** to **1a′**) of H-1/7, H-1′/7′, H-9/11, H-3/5, H-3′/5′ and C-1/7, C-3/5, C-9/11, C-8/12, with **1b** as intermediate. Introduction of **1c** into this mix does not change the qualitative argument, only the observed chemical shifts somewhat, and so can be ignored for now. The shifts for C-8 and C-12 are very similar, and so with this exception, the proposed exchanges are observed. The easiest proton data to analyze is that for H-1/7 and H-1′/7′ since these are simple benzylic AB spectra and the easiest carbon data that from C-1/7 and C-3/5. Then for simple site exchange[16]

$$\Delta G_c^{\ddagger}\ (\mathrm{kcal/mol}) = 2.303 \times 1.9872 T_c (10.319 - \log k_c + \log T_c)$$

where $k_c = (\pi/\sqrt{2})\Delta\nu$ and $\Delta G_c^{\ddagger}$ is the free energy of activation at coalescence.

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[14] Forsyth, D. A.; Sebag, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 9483−9494.

[15] (a) Mitchell, R. H. *Org. Chem.* **1983**, *45*, 239−310. (b) Ernst, L. *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *37*, 47−190. (c) Mitchell. R. H. *J. Am. Chem. Soc.* **2002**, *124*, 2352−2357. (d) Satou, T.; Shinmyozu, T. *J. Chem. Soc., Perkin. Trans. 2* **2002**, 393−397.

[16] Calder, I. C.; Garratt, P. J. *J. Chem. Soc. B* **1967**, 660.

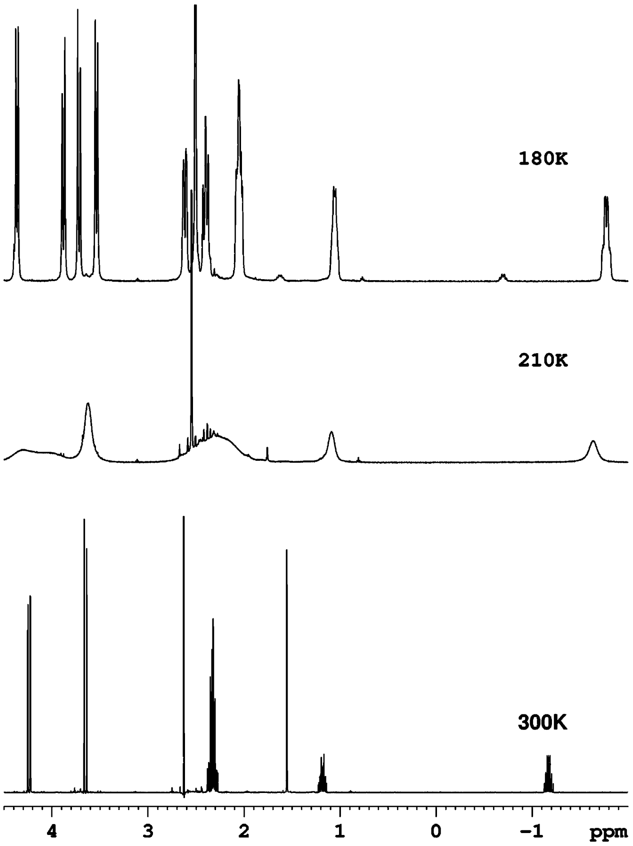

FIGURE 3. ^{1}H NMR spectra of **1** at 180, 210, and 300 K for the protons between δ 4.5 and δ -2. At 180 K, from left to right can be seen [H-1′, H-7′]; [H-7, H-1]; [H-5′, H-3′; H-5/H-3]; H-4; H-4′ (where brakets surround exchangeable protons).

TABLE 5. Coalescence Data for 1

no.	$\Delta\nu$ (Hz)^a	k_c	$T_c{}^b$	$\Delta G_c^{\ddagger c}$
H-1/7	91.1	214	205	9.7
H-1′/7′	242.6	543	210	9.5
C-1/7	226.4	503	215	9.8
C-3/5	563.4	1252	220	9.6

^{a} At 180 K. ^{b} ±3 K. ^{c} kcal/mol, ± 5% typically.[15]

Note that since the exchanging protons H-1/7 are not actually coupled to each other, then the correction for coupled spectra $k_c = (\pi/\sqrt{2})[(\nu_A - \nu_B)^2 + 6J^2]^{1/2}$ does not apply.

The T_c method works as well as detailed line shape analysis in thiacyclophanes[17] and so is applied here. The relevant data are in Table 5 and yield a value of about 9.6 kcal/mol for $\Delta G_c^{\ddagger}$, which is 1−2 kcal/mol lower than the values for the all carbon [7]metacyclophanes[15a,b] but otherwise consistent with them.

It is possible to use the Boltzmann distribution of conformers in Table 3 and the calculated chemical shifts of each conformer from Table 4 to predict chemical shifts for the mixture of conformers of **1** that would be expected at ambient temperatures. In fact, however, the chemical shift differences between **1a** and **1b** (the two dominant conformers) are not very great for most protons and carbons, and only selected values are shown in Table 6.

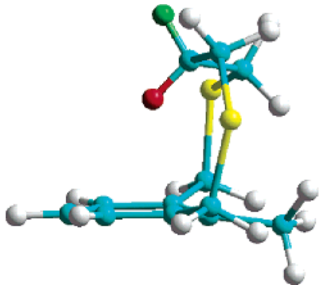

FIGURE 4. Transition structure **1***.

TABLE 6. Selected Calculated and Experimental Chemical Shifts of 1 at 175 and 300 K

no.	δ(175 K)$_{calc}$	δ(300 K)$_{calc}$	δ(175 K)$_{exp}$	δ(300 K)$_{exp}$
H-4	−1.92	−1.22	−1.79	−1.17
H-4′	0.71	0.83	1.06	1.18
H-1,7	3.30	3.31	3.70	3.65
H-1′,7′	3.70	3.74	4.03	4.23
C-4	32.12	33.71	29.23	31.65

Because of the difference between calculated and observed shifts, it is best to compare the change that occurs on changing temperature. For example, increasing the temperature from 175 to 300 K deshields H-4 by about 0.6 ppm and also H-4′ by about 0.1 ppm both for the observed and calculated shifts. Similarly, C-4 is also deshielded about 1.5 ppm. For exchanging protons, e.g., H-1,7 (or H-1′,7′), the average shift of the pair at low temperature is used.

Overall, the good agreement in trend gives confidence that our assignments are correct. As well, in the 180 K spectrum (Figure 3), a small peak at δ -0.7 can be seen; this is consistent with the calculated value for H-4 in **1b**. This suggests then that the exchange occurs **1a** to **1b** to **1a′**, although other conformers will also be involved at higher temperatures.

The quadratic synchronous transit (QST) method (B3LYP/6-31G*) as instituted in Jaguar 4.0[18] was used to search for the transition structure between **1a** and **1b**. The resulting species (**1***) was reoptimized (to a transition state) using G98, B3LYP/6-31G*. Analytical energy second derivatives were calculated and confirmed that **1*** is a transition structure (one imaginary frequency). The intrinsic reaction coordinate (IRC) was run in G98, and the results support our designation of **1*** (Figure 4) as a transition structure for **1a** to **1b**. The calculated free energy of activation of 8.61 kcal/mol is almost identical to that determined from the VT-NMR experiments for **1a** to **1b** to **1a′**. This excellent agreement should give much credibility to the idea that the methods used to obtain our calculated results are valid and reliable.

***tert*-Butyl Phane 2.** In principle, the *tert*-butyl-substituted phane **2** should display the same conformational properties as **1**, since the *tert*-butyl group is well distant from the bridge. Low-level calculations indicate that the same conformers are involved for **2** as for **1**. Due to the added computational expense of this larger system and the expectation of exactly equivalent results to those found for **1a**, only the corresponding conformer to **1a**, namely **2a**, was optimized in G98 using the B3LYP/6-

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[17] Dixon, K. R.; Mitchell, R. H. *Can. J. Chem.* **1983**, *61*, 1598−1602.

[18] Jaguar v 4.0, Schrödinger, Inc., Portland, OR, 1991−2000.

31G* method. Proton and carbon chemical shifts were calculated for **2a** in the same way as for **1a** above. Again, H-4 was calculated to be highly shielded at δ −1.93, with the 175 K value being δ −1.79. Full data are available in the Supporting Information section. One practical advantage of **2**, however, is that the aromatic region of the ^{1}H NMR spectrum is simplified, and H-9/11 appear as a singlet at δ 7.10 at 300 K. As expected, this signal splits in to two singlets at δ 7.11 and 6.93 at 180 K, where $\Delta\nu = 89.83$ Hz, $T_c \approx 205$ K, and $\Delta G_c^{\ddagger} = 9.7$ kcal/mol, in excellent agreement with the value determined for **1**. The benzylic proton pairs H-1/7 and H-1′/7′ likewise yielded $\Delta G_c^{\ddagger}$ values of 9.5 and 9.7 kcal/mol, confirming that the same process is taking place in **2** as in **1**. In the carbon spectra, the only aromatic carbon (with H attached), C-9/11, are at δ 125.70, and as expected these collapse and reemerge as two carbons at δ 124.61 and 123.91 at 180 K. Full spectra and data (for both protons and carbons) for **2** are available in the Supporting Information. Although crystals of **2** were obtained, an unusual crystallographic disorder prevented a solution to the diffraction experiment, which hinders a similar comparison to calculated values.

Summary and Conclusions

We have demonstrated here that, with care, DFT calculations using the B3LYP/6-31G* method can satisfactorily predict the lowest energy conformers of a dithia[7]metacyclophane. Detailed comparison of calculated and experimental proton and carbon chemical shifts, bond distances and angles and activation barriers verify that the calculations perform very well in such a cyclophane with a limited number of conformers. We anticipate that studies such as this will improve the confidence levels that organic chemists will have in such calculations.

Experimental Section

10-*tert*-Butyl-13-methyl-2,6-dithia[7]metacyclophane 2. 1,3-Bis(bromomethyl)-5-*tert*-butyl-2-methylbenzene[19] (2.00 g, 5.99 mmol) and 1,3-propanedithiol (0.61 mL, 5.99 mmol) in benzene (250 mL, well degassed with argon) were added dropwise (~1 drop/s) to a well-stirred solution of KOH (2.1 g, 37 mmol) and $NaBH_4$ (0.3 g, 8 mmol) in ethanol−water (1.5 L/0.15 L, well degassed with argon) under argon, with stirring continued for a total of about 24 h. After removal of solvents, the residue was extracted with dichloromethane, and then the extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed over silica gel (Merck, 60−200 mesh) using hexane−dichloromethane (2:1) as eluant and yielded 360 mg (20%) of white crystals of **2**: mp 91−93 °C (cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$−CD_2Cl_2 (1:3), 300 K) δ 7.10 (s, 2, H-9,11), 4.22 and 3.64 (AB, $J = 12.6$ Hz, H-1,7), 2.58 (s, 3, CH_3-14), 2.39−2.21 (m, 4, H-3,5), 1.29 (s, 9, −C(CH_3)$_3$), 1.17−1.09 (m, 1, H-4′), −1.11 to −1.20 (m, 1, H-4) (see the Supporting Information for VT spectra); ^{13}C NMR (125.8 MHz, $CDCl_3$−CD_2Cl_2 (1:3), 300K) δ 150.4 (C-10), 138.6 (C-8,12), 134.6 (C-13), 125.7 (C-9,11), 36.3 (C-1,7), 34.5 (C(CH$_3$)$_3$), 31.6 (C(CH$_3$)$_3$), 31.0 (C-4), 29.3 (C-3,5), 18.1 (C-13-CH$_3$) (see the Supporting Information for VT spectra); EI MS *m/z* 280 (M^+). Anal. Calcd for $C_{16}H_{24}S_2$: C, 68.51; H, 8.62. Found: C, 68.20; H, 8.41.

13-Methyl-2,6-dithia[7]metacyclophane 1. This was prepared using 1,3-bis(bromomethyl)-2-methylbenzene[20] as described for **2** above (which is similar to the method used by Vögtle[5]), and the yield averaged about 40%: white crystals; mp 70−72 °C (lit.[5] mp 71−72 °C); ^{1}H NMR (500 MHz, $CDCl_3$−CD_2Cl_2 (1:3), 300 K) δ 7.09 (d, $J = 7.4$ Hz, 1, H-10), 7.02 (t, $J = 7.4$ Hz, 2, H-9,11), 4.23 and 3.65 (AB, $J = 12.8$ Hz, 4, H-1,7), 2.63 (s, 3, CH_3-14), 2.38−2.27 (m, 4, H-3,5), 1.22−1.14 (m, 1, H-4′), −1.13 to −1.22 (m, 1, H-4) (see the Supporting Information for VT spectra); ^{13}C NMR (125.8 MHz, $CDCl_3$−CD_2Cl_2 (1:3), 300 K) δ 139.4 (C-8,12), 137.8 (C-13), 128.7 (C-9,11), 127.2 (C-10), 36.2 (C-1,7), 31.7 (C-4), 29.6 (C-3,5), 18.9 (C-14) (see the Supporting Information for VT spectra). Note that at low temperature (Table 4) the chemical shift of C-4 falls between those of C-3 and C-5.

X-ray Crystal Structure of 1. Crystals of compound **1** were removed from the flask and covered with a layer of hydrocarbon oil. A suitable crystal was selected, attached to a glass fiber, and placed in the low-temperature nitrogen stream.[21] Data for **1** were collected at 84(2) K using a Bruker/Siemens SMART APEX instrument (Mo Kα radiation, λ = 0.710 73 Å) equipped with a Cryocool NeverIce low-temperature device. Data were measured using omega scans of 0.3° per frame for 40 s, and a hemisphere of data was collected. A total of 1471 frames were collected with a final resolution of 0.84 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART[22] software and refined using SAINTPlus[23] on all observed reflections. Data reduction and correction for Lp and decay were performed using the SAINTPlus software. Absorption corrections were applied using SADABS.[24] The structure was solved by direct methods and refined by least-squares methods on F^2 using the SHELXTL program package.[25] The structure was solved in the space group *Pbca* (#61) by analysis of systematic absences. All atoms were refined anisotropically. No decomposition was observed during data collection. Details of the data collection and refinement are given in the Supporting Information.

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Supporting Information Available: VT ^{1}H and ^{13}C NMR spectra for **1** and **2**. Atom coordinates and energies for the DFT-minimized structures **1a**−**f**, **1***, and **2a**. X-ray structure details for **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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