

# Experimental and Theoretical Study of Dithia[*n*]metacyclophanes: Syntheses, Chiroptical Properties, and Conformational Analysis

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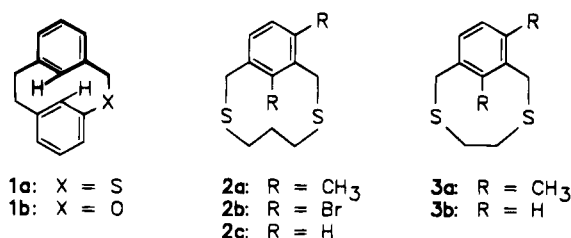
Received August 4, 1994<sup>®</sup>

**Abstract:** The synthesis of 8,12-dimethyl-2,5-dithia[6]metacyclophane (**3a**) has been achieved for the first time by cesium-assisted high dilution methods. Enantiomeric separation was performed by HPLC with enantioselective chromatography using cellulose tris(3,5-dimethylphenyl carbamate). The CD spectra of **3a** and the homologous 9,13-dimethyl-2,6-dithia[7]metacyclophane (**2a**) are reported and compared with results of theoretical AM1/MRD-CI calculations. The geometries of the cyclophanes have been investigated with X-ray and theoretical AM1 and ab initio SCF methods. Application of all these methods reveals the existence of several energetic low-lying conformers with different orientation of the S-(CH<sub>2</sub>)<sub>*n*</sub>-S (*n* = 3 and 2) chains. Comparison of experimental and theoretical CD data shows that the spectra depend strongly on the varying dihedral angles in these chains. Electronic excitations out of the sulfur 3p lone-pair orbitals are quite important in the theoretical description of the Cotton effects above 200 nm excitation wavelength. The conversion barriers (≈20 kJ/mol for **2a**, 40–50 kJ/mol for **3a**) between the conformers have been determined by temperature dependent NMR spectroscopy and are found to be in good agreement with theoretical AM1 data.

## 1. Introduction

The circular dichroism (CD) of large polyatomic molecules containing one or more benzene chromophores has been analyzed in the past with simple models, e.g., quadrant, octant, and sector rules.<sup>1–8</sup> The presence of chromophores with well-defined orientation and large electric dipole transition moments enables application of the exciton–chirality method<sup>9–11</sup> for the prediction of absolute configurations of the enantiomers. The knowledge of absolute configurations is of particular importance in biological and pharmacological studies.<sup>12</sup> Experimentally, the possibilities for extracting this information are restricted and often insufficient. Well-founded theoretical approaches are therefore desirable for the determination of these data. To date, only a few calculations of CD data (transition energies  $\Delta E$  and

Chart 1



rotatory strengths *R*) for larger molecular systems (i.e., >benzene) have been published.<sup>13,14</sup> This is mainly due to the fact that the quality requirements for the wave functions of the ground and excited states are very high, and the electric ( $\mu$ ) and magnetic dipole ( $m$ ) transition moments both have to be obtained to similar accuracy. Single-CI (configuration interaction) calculations with the semiempirical CNDO/S Hamiltonian of extended  $\pi$ -systems with conformational flexibility have been reported.<sup>15,16</sup> However, as a consequence of the CNDO integral approximation this approach is expected to give poorer results for compounds with heteroatoms (N, O, S) for which excitations out of lone-pair orbitals become important.

Recently, we have reported AM1/multireference single + double excitations CI (MRD-CI) calculations based on localized orbitals for rigid thia- and oxa[2.2]metacyclophanes<sup>17</sup> (see Chart 1, compounds **1a** and **1b**). Satisfactory agreement between theory and experiment for the CD spectra has been obtained

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with this new combination of methods. However, many interesting molecules are not conformationally rigid. Such compounds represent a major challenge for the theoretical prediction of CD spectra since CD is often very sensitive to small changes in the conformation of flexible systems. For alkyl-substituted sulfides and disulfides this sensitivity has been used to develop a sector model for the determination of dihedral angles in C-S-C-R<sup>8</sup> or R-S-S-R<sup>7</sup> units. Comparison of calculated and experimental CD spectra of similar systems should provide complementary information to traditional NMR methods, thus allowing the determination of the preferred conformations.

In this study we present the results of AM1/MRD-CI calculations in comparison with experimental CD and NMR measurements for flexible dithia[n]metacyclophanes ( $n = 7$ , **2a**;  $n = 6$ , **3a**; see Chart 1). Ab initio SCF, AM1, and X-ray data for the geometries are presented to determine the structures of the conformational minima and to evaluate the performance of the theoretical models. Molecules with a reduced number of aromatic chromophores (**2a** and **3a**) were synthesized in order to simplify the analysis of the CD spectra. As opposed to **1** only one benzene ring contributes to the CD, and some of the transitions involving the C-S-C units are well separated from other CD bands.

Particular attention was paid to determine the equilibrium ratios of energetically close conformers in solution by comparison of experimental and theoretical CD data.

## 2. Theoretical Methods

All calculations with the AM1-Hamiltonian<sup>18</sup> were performed with a modified version of the MOPAC 6.0 program system.<sup>19</sup> Ab initio SCF calculations were performed with the TURBOMOLE package.<sup>20</sup> The basis sets are of split-valence quality (SV + d, [4s3p]/[3s2p]/[2s] for S, C, and H)<sup>21</sup> augmented with polarization d-functions at the sulfur ( $\alpha_d = 0.55$ ) and carbon ( $\alpha_d = 0.8$ ) atoms. The calculation of transition energies and moments for the CD spectra were carried out with the multireference singles + doubles configuration interaction (MRD-CI) calculation scheme of Buenker and Peyerimhoff<sup>22,23</sup> in combination with the semiempirical AM1 basis. As described earlier<sup>17</sup> most of the valence electrons were separated from the correlation treatment with the use of localized orbitals (LMO). Thus, the 28 electrons which are important for describing the excited states (for details of this selection see ref 17) were distributed in all available virtual LMOs. A threshold of  $T = 1 \mu E_h$  was used in the selection of spin-adapted configurations which yielded CI-secular equation sizes of about 20 000–25 000 for the 14 lowest roots. Oscillator and rotatory strengths were calculated exactly in the Löwdin-orthogonalized AM1-AO basis using the lengths formalism as described in ref 17. To allow visual comparison with experiment, theoretical CD spectra were simulated by summing rotatory strength weighted Gaussian curves with  $\Delta E_{FWHM} = 0.3$  eV for each calculated CD transition. Due to the inherent error of absolute AM1/MRD-CI vertical excitation energies  $\Delta E$ <sup>24</sup> the calculated values were consistently

**Table 1.** Deformation Angles  $\alpha$  and  $\beta$  (see Figure 3) of the Dithia[n]metacyclophanes **2a** (conformer A1) and **3a** (conformer C1)

compd/method	$\alpha$ (deg)	$\beta$ (deg)	AM1 strain energy ( $E_s$ ) (kJ/mol)
<b>2a</b> ( $n = 7$ )			
X-ray	13.0	7.5	
AM1-SCF	15.8	5.6	47
ab initio SCF <sup>a</sup>	12.2	6.2	
<b>3a</b> ( $n = 6$ )			
X-ray	15.8	5.6	
AM1-SCF	18.9	6.8	65
ab initio SCF <sup>a</sup>	14.9	7.0	

<sup>a</sup> SV + d basis set.

shifted by 1.3 eV to obtain agreement between theory and experiment for the first bands of **2a** and **3a**.

## 3. Syntheses and Enantiomeric Separation

Previous attempts to prepare intraannularly substituted dithia-[6]metacyclophanes led to very low yields; only the corresponding fluoro derivative was found by mass spectroscopy.<sup>25–27</sup> The optimization of the cyclization reaction by strict application of the high dilution conditions and use of the cesium effect<sup>28,29</sup> under an inert gas atmosphere leads to higher yields of the more strained dithiaphane **3a** (yield 11%) in relation to the less strained (no steric effect of the intraannular methyl group) unsubstituted dithiaphane **3b** (yield 7%).<sup>25–27</sup> The homologous dithia[7]metacyclophane **2b** was prepared under similar conditions.<sup>30</sup> The syntheses of **2a** and **3a** by the cyclization reactions lead to racemic mixtures. The planar chiral dithiaphane **3a** was totally resolved and **2a** enantiomerically enriched<sup>30</sup> by enantioselective chromatographic technique with a cellulose (3,5-dimethylphenyl carbamate) (CDMPC)<sup>31</sup> HPLC column as chiral stationary phase.

## 4. Results and Discussion

The X-ray structures of **2a** and **3a** show typical metacyclophane geometries,<sup>32,33</sup> i.e., “boat-type” deformed benzene rings with out of plane deformation angles  $\alpha$  and  $\beta$  of 13.0–15.8° and 5.6–7.5°, respectively (Table 1). The S-(CH<sub>2</sub>)<sub>n</sub>-S bridges have no symmetry element so that both compounds have C<sub>1</sub> symmetry even in the absence of the extraannular methyl group. With AM1-SCF calculations six (for **2a**) and three conformers (for **3a**) representing minima on the respective potential energy surfaces were located. In the case of **2a** their relative AM1 energies are within 21 kJ/mol, indicating the flexibility of the S-(CH<sub>2</sub>)<sub>3</sub>-S chain. However, the energies of several of the conformers (not shown) are too high for them to contribute to an equilibrium mixture in solution at room temperature (the experimental conditions of the CD measurements) so that only the three (two) conformers of **2a** (**3a**) lowest in energy will be considered here. They are shown schematically in Figures 1 and 2.

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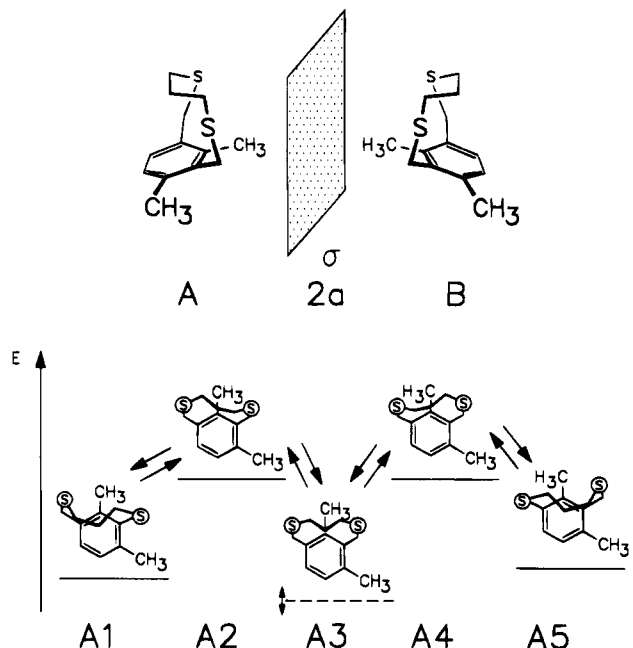
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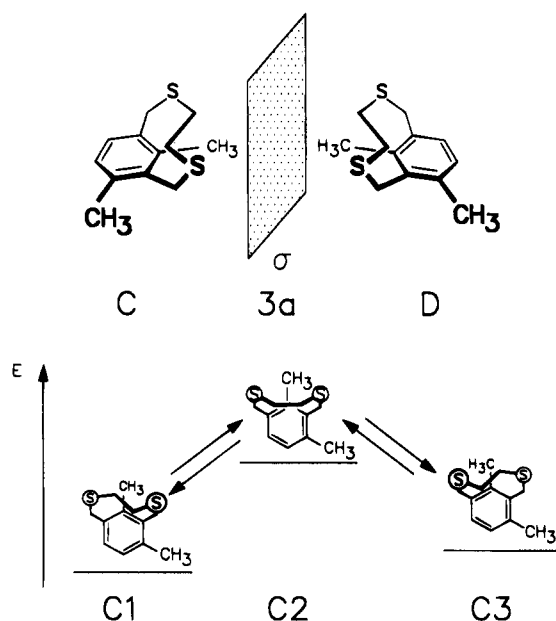
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**Figure 1.** Enantiomers (A and B) and lowest energy conformers (A1–A5) of the enantiomer A of dithia[7]metacyclophane **2a**.



**Figure 2.** Enantiomers (C and D) and lowest energy conformers (C1–C3) of the enantiomer C of dithia[6]metacyclophane **3a**.

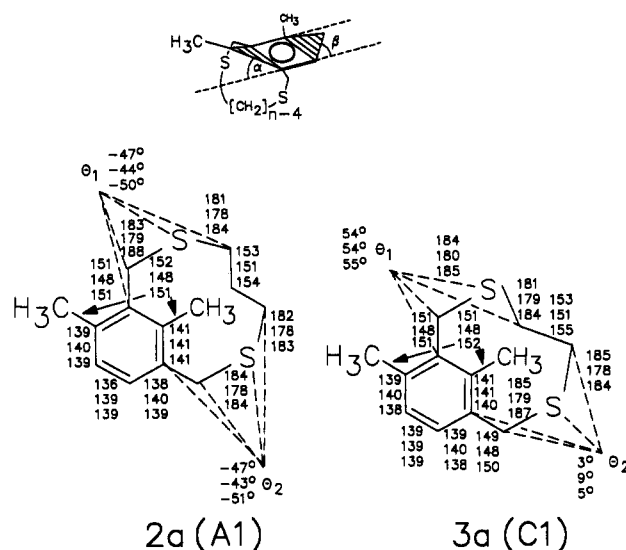
The experimentally found crystal structure of the [6]metacyclophane **3a** corresponds to the conformer **C1** (see Figure 2). At the AM1 level this structure is only 0.4 kJ/mol higher in energy than the diastereomer **C3**. **C3** differs from **C1** in the relative orientation of the two  $C_{ar}-CH_2-S-CH_2$  moieties (dihedral angles  $\theta_1$  and  $\theta_2$ ) with respect to the extraannular methyl group, i.e., the signs of  $\theta_1$  and  $\theta_2$  are interchanged. For **2a** X-ray analysis finds **A1** while the AM1 method predicts **A3** with a symmetric chain to be more stable by 5.7 kJ/mol. The presence of packing effects may alter the relative stabilities so that disagreement here is not unsettling. However, the energy differences are so small at the AM1 level that we decided to perform more sophisticated (but very time consuming) ab initio RHF–SCF optimizations for the various conformers. The results are collected in Table 2.

For **3a** the ab initio calculations find an energy difference between conformers **C1** and **C3** of 1.5 kJ/mol; i.e., as opposed

**Table 2.** Relative Energies (in kJ/mol) of the Conformers of **2a** and **3a**. The Transition States Connecting Them Are Denoted by TS. The NMR Measurements Refer to  $CD_2Cl_2$  Solution

compd	AM1–SCF	ab initio SCF <sup>a</sup>	NMR
<b>2a</b>			
<b>A1</b>	5.7	–7.8	
<b>A2 (TS)</b>	21.7	37.5 <sup>b</sup>	<22–33
<b>A3<sup>c</sup></b>	0.0	0.0	
<b>A4 (TS)</b>	21.4	36.2 <sup>b</sup>	<22–33
<b>A5</b>	5.9	–0.2	
<b>3a</b>			
<b>C1<sup>d</sup></b>	0.0	0.0	0.0
<b>C2 (TS)</b>	41.8	39.1 <sup>b</sup>	≈50
<b>C3</b>	–0.4	1.5	(±)–1.6 ± 0.4 <sup>e</sup>

<sup>a</sup> SV +d basis set. <sup>b</sup> Single point calculation using the AM1 geometries. <sup>c</sup> AM1 heat of formation is 43.79 kJ/mol. The total ab initio SCF energy is –1297.132 24 au. <sup>d</sup> AM1 heat of formation is 94.09 kJ/mol. The total ab initio SCF energy is –1258.120 66 au. <sup>e</sup> Estimated  $\Delta G^{223}$  from the **C1/C3** NMR signal ratio. The sign is experimentally unknown.



**Figure 3.** Comparison of X-ray (top), AM1–SCF (middle), and ab initio SCF (bottom) calculated geometrical parameters of **2a** and **3a**.

to the AM1 result **C1** becomes more stable. In the case of **2a** ab initio theory predicts **A1** to be more stable than the symmetric conformer **A3** by 7.8 kJ/mol. The energy difference between **A1** and **A5** is found to be much larger compared to the AM1 result (7.6 kJ/mol). In summary, comparison of the data show that the semiempirical approach correctly predicts these conformers to fall in a very narrow energy range of several kJ/mol. Due to the neglect of electron correlation and zero-point corrections the ab initio results are also not decisive if such small energy differences are involved. Taking solvation effects (which may be energetically of the same order of magnitude) present in the CD measurements into account we conclude that these standard quantum chemical approaches cannot predict the relative stabilities with sufficient accuracy. Thus we conclude that the energy difference **C1/C3** is zero within the error limits of the MO methods.

The agreement of experimental and theoretical structural data for the geometries (see Figure 3 and Table 1) is quite good, especially for the dihedral angles  $\theta$  (differences are <4 degrees) in the aliphatic chains which are of particular importance for the CD spectra (see below). The AM1 calculated deformation angles  $\alpha$  and  $\beta$ , which give a good measure of the strain energy in cyclophane molecules, are slightly too high, a fact which is well-known in the literature.<sup>34,35</sup> However, the relative increase

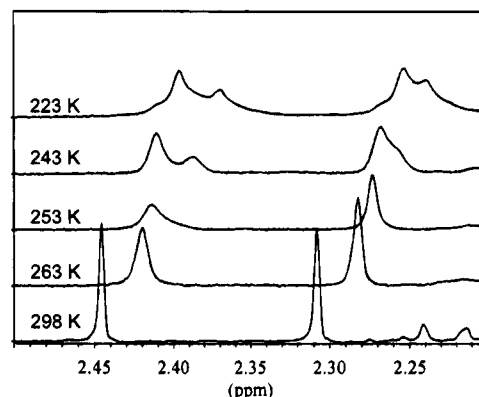
in  $\alpha$  of 3 degrees with shortening of the  $(\text{CH}_2)_{n-4}$  chain by one unit is found by the calculations. At the AM1 level the C–S bond lengths are generally  $\approx 5$  pm too short compared to ab initio or X-ray data which compare quite favorably with each other. The ab initio data are of predictive quality for all geometric variables. However, it should be mentioned that the AM1 geometries are quite useful for the calculations of the CD spectra since small systematic deviations in bond lengths are not an important factor. CD spectra obtained with AM1 or X-ray geometries are nearly indistinguishable from another since the dihedral angles in the aliphatic chain are equal to within  $2-3^\circ$ .

Strain energies of both compounds were calculated at the AM1 level with the unstrained reference systems 1,2,3,4-tetramethylbenzene and the corresponding bis(methylthio)alkanes. The resulting values of 47 (**2a**) and 65 kJ/mol (**3a**) are similar to those of [9]- and [8]paracyclophanes (40 and 67 kJ/mol, respectively<sup>35</sup>) indicating significant strain in the molecules.

The  $^1\text{H}$ -NMR spectra of **2a** and **3a** show two AB spin systems between 3.5 and 4.5 ppm with a coupling constant of  $\approx 12$  Hz. These signals result from the benzylic protons (geminal coupling) which have frequently been used in such cyclophane compounds to detect the motion of the aliphatic chain to the opposite side of the benzene ring.<sup>32</sup> Here, the intraannular methyl group prevents such conformational flexibility which is deduced from the absence of any temperature dependence of NMR signals of **2a** up to 400 K. This is also found for **3a** which seems obvious considering the smaller ring size in this compound.

The conformers **A1** and **C1** have diastereomeric counterparts (**A5** and **C3**), and they would be enantiomers in the absence of the extraannular methyl group. It is important to mention here that the extraannular substituent breaks the mirror image relationship between unsubstituted **A1/A5** and **C1/C3**. However, this symmetry breaking effect is very small which is clearly seen by the negligible AM1 energy differences between **C1/C3** (0.4 kJ/mol) and **A1/A5** (0.2 kJ/mol). On the other hand, this effect may be stronger for the wavefunctions (especially in the excited states) which will be indicated by the comparison of calculated CD spectra. We will show below that weak perturbations of the inherent chiral chromophores (the C–S–C units) result in small but significant differences in the CD spectra of the pairs **C1/C3** and **A1/A5**.

The energetic barriers separating the diastereomers have been calculated at the AM1 level by complete optimizations of the corresponding transition states (TS, characterized by one imaginary vibrational frequency) and by single point ab initio calculations with the AM1 geometries. For **2a** a small barrier of 21.7 kJ/mol between **A1** and **A3** was found. Indeed, consistent with this prediction we were unable to detect any temperature dependence in the NMR signals of **2a** down to 200 K. This yields an estimate of the upper limit of the barrier of 22–33 kJ/mol (assuming an Arrhenius frequency factor of  $10^9$ – $10^{12}$  s $^{-1}$ ). In the case of **3a** the AM1 data are also of predictive quality. The barrier separating **C1** and **C3** is calculated to be 41.8 kJ/mol so that NMR spectroscopy should detect a temperature dependence in the spectra. This is indeed found and shown in an exemplary manner for the methyl group protons of **3a** in Figure 4. At room temperature two sharp signals for the two methyl group protons are observed at averaged positions while at low temperatures different signals for **C1** and **C3** occur.



**Figure 4.** Temperature dependent  $^1\text{H}$ -NMR spectra of **3a** in  $\text{CD}_2\text{Cl}_2$  (400 MHz). The signals correspond to the intraannular and extraannular methyl groups.

Quantitative analysis of these NMR spectra by inserting the coalescence temperature ( $T_c = 248$  K) and the maximal splitting of the two signals ( $\Delta\nu = 12$  Hz) into a simplified Bloch/Eyring equation<sup>36</sup> give a barrier height of  $\approx 50$  kJ/mol. Integration of the signals of the two conformers at 223 K (the portion of the more stable conformer at this temperature is  $70 \pm 5\%$ ) gives a free enthalpy difference of  $1.6 \pm 0.4$  kJ/mol. Unfortunately, the NMR measurements do not allow an assignment of which of the two conformers (**C1** or **C3**) is more stable in solution. The ab initio calculated barriers with the AM1 optimized geometries (Table 2) are very similar to the AM1 and experimental data revealing the success of the semiempirical method and the applicability of AM1 geometries for single point calculations with only minor loss of accuracy.

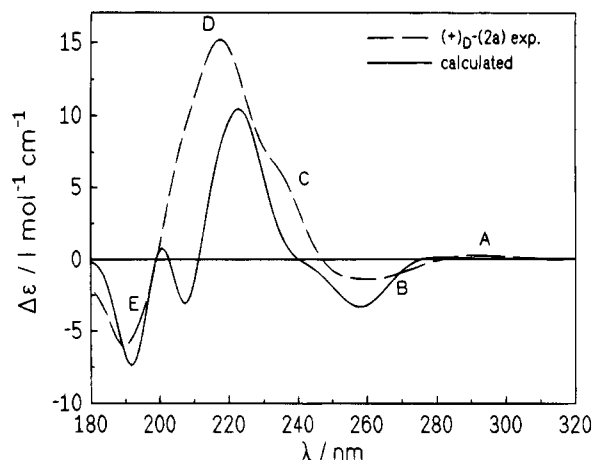
To analyze the conformational dependence of the CD spectra theoretically we make the following assumptions: first, there is an equilibrium mixture of the conformers **A1** and **A5** or of **C1** and **C3**. The calculated CD spectrum of **A3** has very low intensity in the measured energy range due to the symmetric orientation of the S–C–C–C–S chain so that it is omitted in this analysis. The CD spectra are only calculated for the respective minima, thus neglecting the width of the vibrational wavefunctions with respect to  $\theta$  and the temperature dependent occupation of the vibrational levels. For **3a** this seems to be a good approximation due to the relatively high barrier while it seems very unlikely in the case of **2a** where the barrier is probably below 25 kJ/mol.

Now let us discuss the CD spectra in comparison with the theoretical AM1/MRD-CI calculations which allow a certain assignment and interpretation of the transitions involved in a particular CD band. The experimental CD spectra of the **2a** and **3a** in the range 180–320 nm (see Figures 5 and 6) are very similar and show five distinct bands A–E. The first of these with a maximum at 290–300 nm is very weak and is easily attributed to the first  $\pi\pi$  ( $L_b$ ) state of the benzene ring. The calculated rotatory strengths ( $R$  values, in the following given in  $10^{-40}$  cgs units) are negligible ( $-0.2$ ) which comes from the fact that this transition, which is magnetically and electrically dipole forbidden in benzene itself, borrows intensity by vibronic coupling which is absent in our theoretical investigation (Figure 7). The next band around 260 nm (**B**) has opposite sign. The most intense part of the spectra follows between 200 and 240 nm. Here, a significant difference between **2a** and **3a** is seen; namely, the splitting of the C and D bands is significantly larger in the latter compound. Again, the last band E shows opposite sign with respect to the lower-lying transitions.

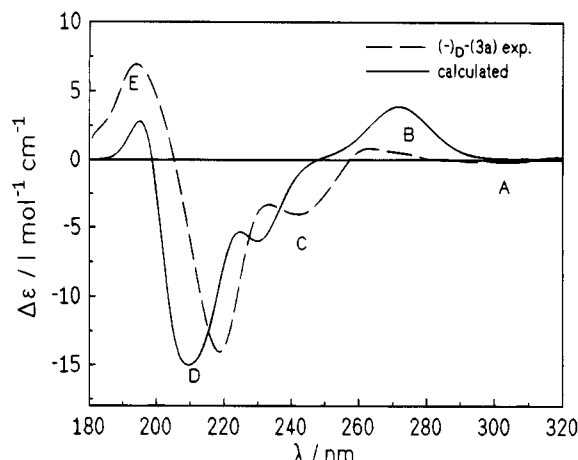
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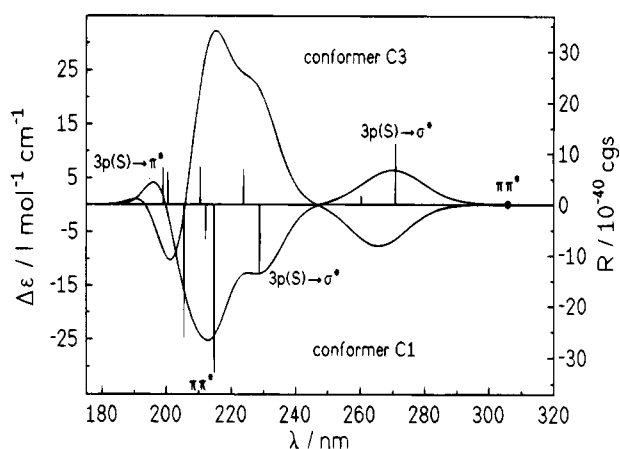
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**Figure 5.** Comparison of calculated (AM1/MRD-CI) and experimental (in *n*-hexane) CD spectra of **2a**.

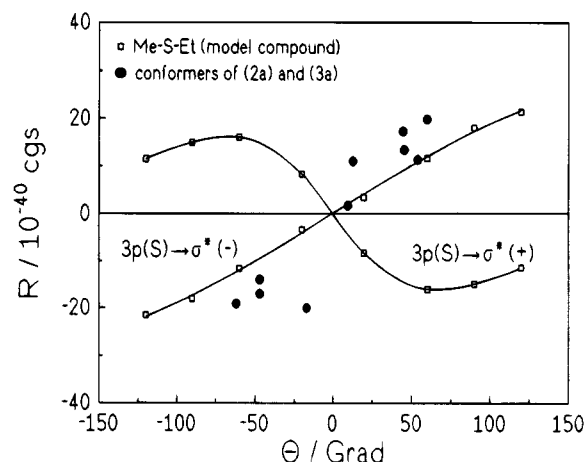


**Figure 6.** Comparison of calculated (AM1/MRD-CI) and experimental (in *n*-hexane) CD spectra of **3a**.



**Figure 7.** Calculated CD spectra of the conformers **C1** and **C3** of **3a**. The positions and rotatory strengths of the transitions of **C3** are designated by sticks. The filled point indicate the lowest  $\pi\pi^*$  excited state with near zero  $R$  value.

As found previously for thia[2.2]metacyclophanes<sup>17</sup> the CD spectra of sulfur-containing cyclophanes are strongly affected by transitions which are characterized by excitations out of the sulfur lone-pair orbitals (mainly 3p) in antibonding C–S  $\sigma^*$  MOs. Here we have two of these transitions at about 250–270 nm, slightly split (by 0.1 eV) and attributed to local excitations corresponding with the two sulfur atoms. Due to the presence of two different C–S bonds a second set of 3p  $\rightarrow \sigma^*$  states is observed at higher energies (220–240 nm). The



**Figure 8.** Dependence of the rotatory strengths for the 3p(S)  $\rightarrow \sigma^*(+)$  and 3p(S)  $\rightarrow \sigma^*(-)$  transitions of the model compound ethyl methyl sulfide (open circles) and the conformers of the dithiametacyclophanes **2a** and **3a** (filled circles) on the dihedral angle  $\theta$ .

latter states can be interpreted as positive linear combinations (denoted by  $(+)$ ) of the excitations into the two C–S bonds while the former at lower energies are 3p  $\rightarrow \sigma^*(-)$ . Transitions of this type have been investigated by Snatzke et al.<sup>8</sup> in simple alkyl sulfides, and a quadrant rule for the low energy states  $(-)$  could be derived from group theoretical analysis. In accordance with this rule one can alternatively use a dihedral angle  $\theta$  in the R–C–S–C unit which determines the position of the perturbative substituent R (for  $\theta = 0$  the system has  $C_s$  symmetry and the CD vanishes). We have carried out AM1/MRD-CI calculations with the model chromophore ethyl methyl sulfide at several values of  $\theta$ . As shown in Figure 8 the results agree with the quadrant rule of Snatzke. In the dithia[n]-metacyclophanes the perturbing substituent R is represented by the aromatic ring so that the rotatory strengths of the 3p  $\rightarrow \sigma^*(-)$  transitions calculated for various conformers of **2a** and **3a** fit nicely with the curve of the model compound (the filled dots in Figure 8). The higher excited 3p  $\rightarrow \sigma^*(+)$  states on the other hand show significant mixing with 3p  $\rightarrow \pi\pi^*$  charge transfer states so that no simple rule could be given there. Along with the nearly pure  $\pi\pi^*$  states of the aromatic ring they form the C and D bands.

As a consequence the mid energy range of the CD spectra of **2a** and **3a** is strongly determined by the sign and the magnitude of the dihedral angle C<sub>ar</sub>–C–S–C ( $\theta$ ) which varies considerably among the conformers. Since the diastereomeric counterparts **C1/C3** and **A1/A5** have nearly the same  $\theta_1$  and  $\theta_2$  but of opposite sign we expect a cancellation of these CD bands. That this also holds for the high energy transitions is shown by comparison of the calculated CD spectra of the conformers **C1** and **C3** in Figure 7. The spectra are nearly mirror images (larger deviations occur below 200 nm) which is explained by the small perturbation of the inherent chiral C–S–C chromophores by the extraannular methyl group. As discussed above an equilibrium mixture of **C1** and **C3** conformers accounts for the experimental room temperature CD spectra of **3a**. The best agreement between theory and experiment (see Figure 6) is obtained by a summation of the calculated spectra with a mixture of 80% (**C1**) and 20% (**C3**) which compares quite nicely with the NMR data (the portions are 70/30%). Significantly-poorer agreement is found for a mixture with 20% (**C1**) and 80% (**C3**) indicating that **C1** seems to be more stable in solution. This finding agrees with ab initio relative stabilities and X-ray data but contradicts the AM1 results. Not only the general shape and individual bands but also the absolute  $\Delta\epsilon$  values agree very

well with each other. Application of this procedure to the spectrum of **2a** (60% **A1** and 40% **A5**, see Figure 5) shows significantly poorer agreement. The reason seems not to be the neglect of the **A3** conformer (the calculated CD intensities for this compound are smaller by a factor of 10 due to the symmetric arrangement of the chain, i.e.,  $\theta_1 \approx -\theta_2$ ) but the lower barriers separating **A1** and **A5**. Here large amplitude torsion motions in the S-(CH<sub>2</sub>)<sub>3</sub>-S chain occur, a fact which does not permit the neglect of the vibrational wavefunctions in the theoretical treatment.

## 5. Experimental Section

**1,3-Bis(bromomethyl)-2,4-dimethylbenzene. Procedure:**<sup>37</sup> 2,6-Dimethylbenzyl alcohol<sup>38</sup> (13.6 g, 0.1 mol) was added to a mixture of 47% aqueous HBr (50 mL) and glacial HOAc (15 mL), followed by 1,3,5-trioxane (6 g, 66.7 mmol) and tetradecyltrimethylammonium bromide (1 g). The mixture was then well stirred such that only a single layer could be seen and then heated to a gentle reflux for 24 h. After being cooled to room temperature, the milky solid was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was well washed with water and dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent evaporated. The residue was chromatographed (silica gel 63–100  $\mu$ m; CH<sub>2</sub>Cl<sub>2</sub>/light petroleum bp 40–60 °C, 1:1,  $R_f$  = 0.78) to give 2.39 g (82%) of the product; mp 69 °C. MS (70 eV)  $m/z$ : 289.9306 (11) [M<sup>+</sup>], calcd 289.9306, 211 (97) [M<sup>+</sup> - Br], 132 (100) [M<sup>+</sup> - 2Br], 117 (26) [132 - CH<sub>3</sub>], 91 (17) [C<sub>7</sub>H<sub>7</sub>]. <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  2.41 (s, 3H, CH<sub>3</sub>), 2.44 (s, 3H, CH<sub>3</sub>), 4.51 (s, 2H, CH<sub>2</sub>), 4.57 (s, 2H, CH<sub>2</sub>), 7.02 (d, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, 1H, ArH), 7.19 (d, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, 1H, ArH). <sup>13</sup>C-NMR (62.89 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  14.57 (CH<sub>3</sub>), 19.72 (CH<sub>3</sub>), 29.19 (CH<sub>2</sub>), 33.12 (CH<sub>2</sub>), 128.56 (CH), 130.53 (CH), 134.45 (Cq), 135.27 (Cq), 137.01 (Cq), 138.64 (Cq).

**8,12-Dimethyl-2,5-dithia[6]metacyclophane (3a). Solution 1:** 1.46 g of 1,3-bis(bromomethyl)-2,4-dimethylbenzene (5 mmol) was dissolved in 50 mL of dry and degassed benzene. **Solution 2:** 1.49 g of cesium hydroxide (10 mmol) and 0.47 g of 1,2-ethanedithiol (5 mmol) was dissolved in 50 mL of absolute and degassed ethanol. Solution 1 and 2, then, were simultaneously and separately dropped into a boiling stirred mixture of 300 mL of absolute and degassed ethanol and 600 mL of dry and degassed benzene in the reaction flask under nitrogen atmosphere. A medical perfusor with two 50 mL syringes was used as a two-component high-dilution apparatus.<sup>39</sup> The velocity of dropping was 5 mL/h and the resulting dropping time was 10 h. After the mixture had been refluxed for an additional 4 h, the solvent was evaporated and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The cesium bromide was extracted with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated,

and chromatographed (silica gel 63–100  $\mu$ m; CH<sub>2</sub>Cl<sub>2</sub>/light petroleum bp 40–60 °C, 1:1,  $R_f$  = 0.51) to give 120 mg (11%) of **3a**; mp 74–75 °C. MS (70 eV)  $m/z$ : 224.0695 (15) [M<sup>+</sup>], calcd 224.0693, 163 (69) [M<sup>+</sup> - SC<sub>2</sub>H<sub>5</sub>], 132 (100) [M<sup>+</sup> - SCH<sub>2</sub>CH<sub>2</sub>S], 117 (33) [132 - CH<sub>3</sub>], 91 (11) [C<sub>7</sub>H<sub>7</sub>]. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 25 °C/–50 °C\*):  $\delta$  (ppm) –0.59\* (m, 1H, CH<sub>2</sub>), 2.21 (m, 1H, CH<sub>2</sub>S), 2.24 (m, 1H, CH<sub>2</sub>S), 2.31 (s, 3H, CH<sub>3</sub>), 2.45 (s, 3H, CH<sub>3</sub>), 2.65\* (m, 1H, CH<sub>2</sub>), 3.61 (d, <sup>3</sup>J<sub>HH</sub> = 11.1 Hz, 1H, ArCH<sub>2</sub>S), 3.81 (d, <sup>3</sup>J<sub>HH</sub> = 11.8 Hz, 1H, ArCH<sub>2</sub>S), 4.25 (d, <sup>3</sup>J<sub>HH</sub> = 11.8 Hz, 1H, ArCH<sub>2</sub>S), 4.27 (d, <sup>3</sup>J<sub>HH</sub> = 11.1 Hz, 1H, ArCH<sub>2</sub>S), 6.89 (d, <sup>3</sup>J<sub>HH</sub> = 7.3 Hz, 1H, ArH), 6.95 (d, <sup>3</sup>J<sub>HH</sub> = 7.3 Hz, 1H, ArH). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  (ppm) 18.85 (CH<sub>3</sub>), 18.96 (CH<sub>3</sub>), 31.54 (2 CH<sub>2</sub>), 32.28 (CH<sub>2</sub>), 34.99 (CH<sub>2</sub>), 126.80 (CH), 128.61 (CH), 133.23 (Cq), 133.96 (Cq), 134.97 (2Cq).

**Enantiomeric Separation by HPLC.** Column: Cellulose tris(3,5-dimethylphenylcarbamate) (CDMPC),<sup>31</sup> 500  $\times$  4.6 mm. Eluent: *n*-hexane, 0.25 mL min<sup>–1</sup>. Pressure: 2 bar. Detection: UV,  $\lambda$  = 254 nm, 25 °C.  $t_R$ [(–)-**3a**] = 123 min,  $t_R$ [(+)-**3a**] = 134 min.

**X-ray Structure of 3a.** Crystal data: C<sub>12</sub>H<sub>16</sub>S<sub>2</sub>, MW 224.4, colorless crystals, dimensions 0.25  $\times$  0.25  $\times$  0.10 mm, triclinic, space group *P*1 (No. 2),  $a$  = 7.831(2) Å,  $b$  = 8.453(1) Å,  $c$  = 8.598(3) Å,  $\alpha$  = 85.85(2)°,  $\beta$  = 87.97(2)°,  $\gamma$  = 84.84(2)°,  $V$  = 565.1(3) Å<sup>3</sup>,  $Z$  = 2,  $d_{\text{calcd}}$  = 1.32 g  $\times$  cm<sup>–3</sup>,  $\lambda$  (Cu K $\alpha$ ) = 3.90 nm<sup>–1</sup>,  $F(000)$  = 240. A total of 2306 reflections ( $2\theta_{\text{max}}$  = 140°) were recorded on an Enraf-Nonius CAD4 diffractometer at  $T$  = 200(2) K. Of these, 2149 symmetry-independent reflections were used for the structure solution (direct methods) and refinement (129 parameters) using the SHELXL-93<sup>40</sup> program system. Non-hydrogen atoms were refined anisotropically (full-matrix least-squares on  $F^2$ ); H atoms were refined using a riding model,  $wR_2$  = 0.152 ( $R_1$  = 0.051 for  $I > 2\sigma(I)$ ). Largest difference peak and hole 0.35/–0.55 e Å<sup>–3</sup>. An absorption correction was applied using the DIFABS program.<sup>41</sup>

**Acknowledgment.** The services and computer time made available by the Sonderforschungsbereich 334 (Wechselwirkungen in Molekülen) have been essential to the study. This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG). We thank G. Harder, F. Ott, W. Schmidt, and M. Böhme for help with the NMR and CD measurements.

**Supplementary Material Available:** Tables of crystal data, ORTEP plot, final atomic coordinates, anisotropic displacement parameters, and bond lengths and angles (7 pages); listing of final observed and calculated structure factors (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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