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Synthesis and Unusual Crystal Structure of *syn*-6,15-Dicyano-2,11-dithia[3.3]metacyclophane.

Graham J. Bodwell*, John N. Bridson, Tom J. Houghton and Bala Yarlagadda

Chemistry Department, Memorial University of Newfoundland,
St. John's, NF, Canada, A1B 3X7

Abstract: *syn*-6,15-Dicyano-2,11-dithia[3.3]metacyclophane **4** is the first of its kind to crystallize with both bridges in the *pseudo-boat* conformation. A number of other unusual features are also apparent in the crystal structure, none of which are predicted by AM1 or *ab initio* calculations.
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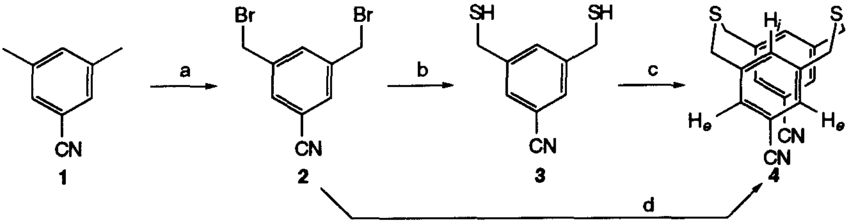
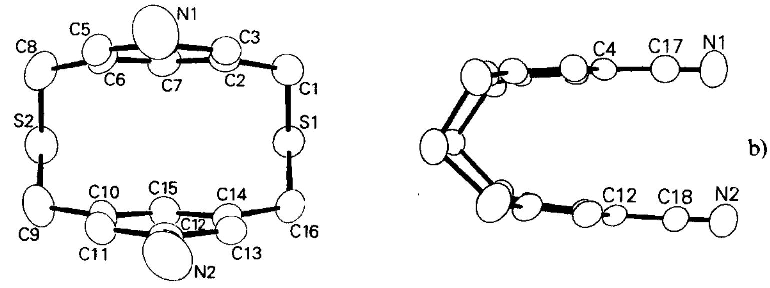
2,11-Dithia[3.3]metacyclophanes are prominent members of the cyclophane family due to their interesting conformational behaviour, unusual spectroscopic properties, transannular interactions and their utility as precursors to [2.2]metacyclophanes and [2.2]metacyclophane-1,9-dienes.[1] For the latter reason, we required *syn*-6,15-dicyano-2,11-dithia[3.3]metacyclophane as a synthetic intermediate in connection with ongoing studies of [n.2.2](1,3,5)cyclophanes ("tethered [2.2]metacyclophanes")[2] and [*n*](2,7)pyrenophanes.[3]

The synthesis (Scheme 1) started with 5-cyano-*m*-xylene **1**, which was brominated with NBS/AIBN/hv to afford dibromide **2** in 40% yield. Conversion of **2** into dithiol **3** proceeded in only 48% yield, presumably due to partial hydrolysis of the nitrile function during the base hydrolysis of the intermediate *bis*-isothiouronium salt. High dilution coupling of **2** and **3** produced the dithiacyclophane **4**[4] in 77% yield. In order to circumvent the problems associated with the hydrolysis step, the self-coupling of **2** using Na_2S/Al_2O_3[5] was investigated as an alternate route to **4**. Analysis of the 300 MHz ^1H NMR spectrum of the crude product indicated that **4** had been formed in the typical 50-60% yield. However, separating it from the corresponding cyclic trimer proved to be very difficult. Careful, repeated chromatography afforded 25% of pure **4**. The internal protons (H_i) of **4** appear at δ 7.31 in its 300 MHz ^1H NMR spectrum, indicating that the molecule adopts the expected *syn* conformation in solution.[6] The bridge protons appear as a singlet at δ 3.72.



Scheme 1. a) NBS, AIBN, hv, CCl_4, Δ, 2h, 40%; b) $(H_2N)_2CS$, EtOH, Δ, 3h, then NaOH, H_2O, Δ, 4 h, 48%; c) **2**, NaOH, $C_6H_6/EtOH/H_2O$, r.t., 48 h, 77%; d) Na_2S/Al_2O_3, $CH_2Cl_2/EtOH$, 24 h, 25%.

Single crystal X-ray analysis of **4**[7] showed that the ring conformation in the solid state was also *syn*. However, much to our surprise, both bridges had adopted the *pseudo-boat* conformation (Figure 2), rendering it the first example of a *syn*-2,11-dithia[3.3]metacyclophane to exist in this conformation in the solid state. A number of other unusual structural features also characterize **4** in the crystal. The aromatic rings do not deviate from planarity significantly, but form an exceptionally low inter-ring angle of 9.0°. By comparison, the bridges of *syn*-2,11-dithia[3.3]metacyclophane **5** are both in the *pseudo-chair* conformation in the solid state and the aromatic rings form an angle of 20.6°.[8] Remarkably, the two cyano groups are bent slightly out of the planes of the aromatic rings *towards* one another. We are aware of no precedent for this effect in face-to-face situated arenes. The C≡N bonds form angles of 3° and 4° with the best planes of the rings they are bonded to. The origin of this most unusual distortion is unclear and will be the subject of further study. Another unusual feature of this structure is the face-to-face slippage of the two aromatic rings in the direction of the C≡N bonds, best seen in the side view in Figure 1. A direct consequence of this is that the two sulfur atoms are closer to the calculated position of one of the internal hydrogen atoms (H_i) than the other. One of them (C15-H)[9] is 2.91 Å away from one sulfur atom and 2.93 Å away from the other, distances which are slightly less than the sum of their van der Waals radii (3.05 Å).[10] The other internal proton (C7-H)[9] is calculated to be 3.07 and 3.12 Å away from the two sulfur atoms. Examination of the crystal packing diagram revealed no noteworthy packing arrangement or intermolecular close contacts.

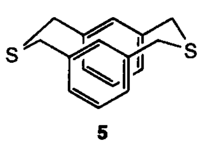


a) back view

b) side view

Figure 1. Two views of **2** in the crystal. Selected distances (Å) and angles (°). C(7)-C(15) 3.152(4), S(1)-S(2) 5.235(2), C(1)-S(1) 1.814(3), C(17)-N(1) 1.141(4), N(1)-N(2) 3.684(4); C(2)-C(1)-S(1) 114.4(2), C(1)-S(1)-C(16) 104.2(1), C(15)-C(12)-C(18) 176.9(2), C(12)-C(18)-N(2) 178.8(3). Note that the crystallographic numbering differs from the systematic numbering.

The only other *syn*-[3.3]metacyclophane derivatives reported to crystallize with both bridges in the *pseudo-boat* conformation are *syn*-1,3,10,12-tetrathia[3.3](2,6)pyridinophane **6**[11] and *syn*-[3.3](2,6)pyridinophane **7** (inter-ring angle = 34°).[12] A dynamic ^{1}H NMR study of **7**[12] provided evidence that the *pseudo-boat,pseudo-boat* conformer was also the most stable in solution. In the case of **6**, N-S repulsions were invoked as the probable cause of the unusual bridge conformations. These same repulsions were also



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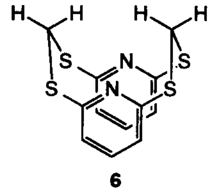

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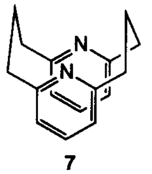

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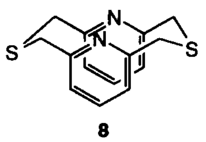

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postulated to be a contributing factor towards the adoption of the usual *pseudo-chair,pseudo-chair* conformation in the crystal structure of *syn*-2,11-dithia[3.3](2,6)pyridinophane **8**.[11] For both **6** and **7**, the short distances between the internal N atoms and the inner hydrogen atoms of the central methylene groups of the bridges (2.5 Å for **6** and 2.50 Å for **7**) suggested the presence of weak hydrogen bonds. In fact, hydrogen bonding was deemed to be the primary cause of the unusual bridge conformations in **7**. While it may be tempting to invoke a weak S-H hydrogen bond in **4**, the hydrogen bond donor (the S atom) is considerably weaker than that of **6** and **7** (an N atom). In addition, if the bridges of **4** were in the *pseudo-chair* conformation, an analogous spatial relationship could exist between the S atoms and the external aryl protons (H_e). As such, it seems unlikely that hydrogen bonding bears any significant responsibility for the observed solid state bridge conformations in **4**.

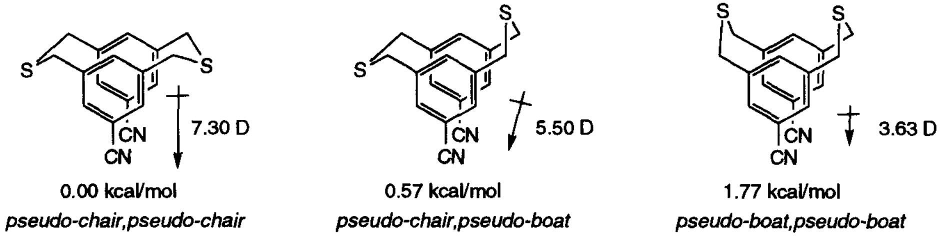

Figure 2. AM1 Calculated Relative Free Energies and Dipole Moments of the Bridge Conformers of *syn*-**4**.

AM1 calculations were performed on the three possible bridge conformers of *syn*-**4** using the Spartan software package (Figure 2). Typical for a [3.3]metacyclophane,[13] the *pseudo-chair,pseudo-chair* conformer was calculated to be the lowest in energy with the *pseudo-chair,pseudo-boat* conformer 0.57 kcal/mol higher in energy and the *pseudo-boat,pseudo-boat* conformer observed in the crystal 1.77 kcal/mol higher in energy (Figure 2). An analogous discrepancy between calculations and observations was also encountered in the study of **7**.[12] Calculations were not reported for the various bridge conformers of **6**, but our own AM1 calculations predict the same order of relative energies. Worthy of note is that the calculated structure of the *pseudo-boat,pseudo-boat* conformer of **4** does not exhibit any of the unusual features observed in the crystal structure. This was also true when *ab initio* calculations were performed on this conformer of **4** at the 3-21G(*) level.

The dipole moments of the three conformers of *syn*-**4** were also calculated. With the sum of the C-S bond dipoles aligned directly against the $C{\equiv}N$ bond dipoles in the *pseudo-boat,pseudo-boat* conformer, it is not surprising that the calculated dipole moment of this conformer (3.63 D) is substantially smaller than those of the *pseudo-chair,pseudo-boat* conformer (5.50 D) and the *pseudo-chair,pseudo-chair* conformer (7.30 D). It may then be that either an inherent dipolar effect within *syn*-**4** or the dipole component of the crystal packing forces is instrumental in determining the bridge conformations in the solid state.

As for the conformational behaviour of **4** in solution, its poor solubility has ruled out dynamic ^{1}H NMR studies so far. Other methods are now being investigated. Whether or not dipolar effects generally influence the relative energies of the bridge conformations of 6,15-disubstituted *syn*-2,11-dithia[3.3]metacyclophanes in solution is also under investigation.

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4. **4**: m.p. 284-288 °C, ^{1}H NMR (300 MHz, CDCl$_3$) $\delta = 7.31$ (s, 2H), 7.13 (d, $J = 1.4$ Hz, 4H), 3.81 (s, 8H); ^{13}C NMR (75 MHz, CDCl$_3$) $\delta = 138.6, 135.2, 130.7, 117.9, 112.8, 37.6$; LRMS (EI, 70 eV), m/z (%) 323 (24), 322 (100, M+), 221 (7), 192 (23), 163 (13), 162 (86), 161 (84), 160 (32), 131 (69), 130 (99), 129 (26), 116 (23), 103 (23); HRMS calcd. 322.0598, found 322.0591.
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7. Crystal data for **4**: colorless single crystal (0.40 x 0.35 x 0.15 mm) from chloroform, $C_{18}H_{14}N_2S_2$, M = 322.44, triclinic, P`1 (#2), Z = 2, $a = 9.229$ (2), $b = 12.783$ (2), $c = 7.151$ (2) Å, $\alpha = 92.90$ (2), $\beta = 109.72$ (2), $\gamma = 102.39$ (1) °, V = 768.6 (3) Å^3, $D_c = 1.393$ g cm^{-3}, F(000) = 336, μ (Mo-Kα) = 3.28 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71069$ Å), ω-2θ scan type with ω scan width = 1.84 + 0.30 tan θ, ω scan speed 8.0° min^{-1} (2 rescans for weak reflections), 2906 reflections measured, 2724 unique ($R_{int} = 0.025$), empirical absorbtion correction (max., min. corrections = 1.05, 0.92), giving 1935 with $I > 2\sigma(I)$. Solution and refinement by direct methods using the TEXSAN package of the Molecular Structure Corporation; all non-hydrogen atoms were refined anisotropically; full matrix least squares refinement with 199 variable parameters led to $R = 0.038$ and $R_w = 0.039$, GOF = 1.73.
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