Pergamon

Tetrahedron Letters 39 (1998) 2231–2234

TETRAHEDRON
LETTERS

Expanded Cyclophanes 1.
Synthesis and Structure of 4,17-Dithia[7.7]metacyclophane-1,6,14,19-tetrayne.

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Received 2 May 1997; revised 20 January 1998; accepted 21 January 1998

Abstract: The title compound **3** was synthesized in three steps from 1,3-dibromobenzene in 26% overall yield. In the solid state, the molecule adopts a twisted *anti* conformation which does not correspond to any known conformation of its lower alkynylogue, 2,11-dithia[3.3]metacyclophane **1**.

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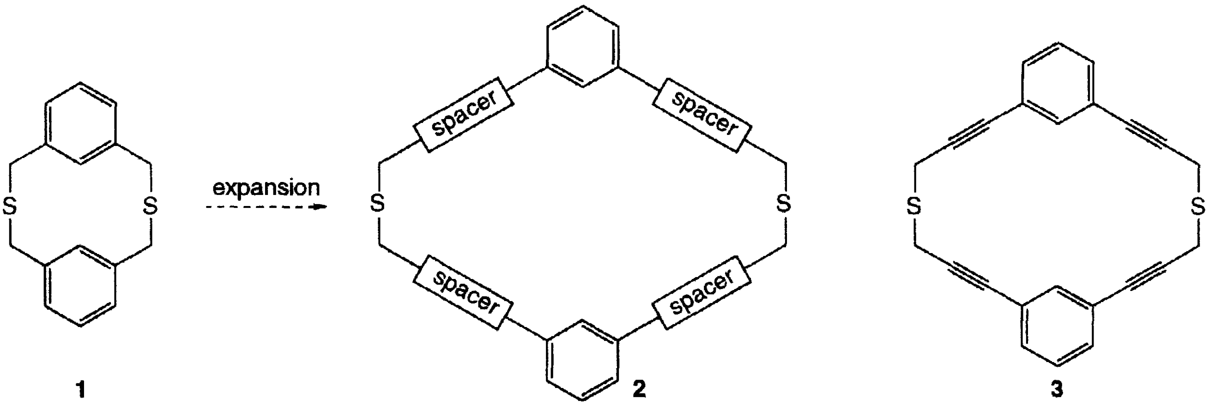
In connection with an ongoing study of novel cyclophanes,[1,2] we have recently become interested in the synthesis and study of cyclophanes containing rigid spacers in their bridges, e.g. **2** (Scheme 1). Our initial interest in this area is directed towards the development of expedient synthetic routes to these "expanded cyclophanes" and determining whether or not their conformational behavior mirrors that of their well studied parent cyclophanes.[3] Our first choice of targets was the title compound **3**, which is derived from the insertion of an alkyne spacer into each of the aryl-benzyl C-C bonds of 2,11-dithia[3.3]metacyclophane **1** and we now report our initial results.



Scheme 1.

The synthesis of **3** (Scheme 2) started with 1,3-dibromobenzene **4**, which was subjected to a two-fold Heck reaction[4] with propargyl alcohol to afford diol **5** in 67% yield. Treatment of **5** with CBr_4/PPh_3 then gave dibromide **6** in 94% yield and reaction of this with Na_2S/Al_2O_3[5] provided the desired dithiacyclophane **3**[6,7] in 42% isolated yield. Careful chromatography was required to separate **3** from another product, presumably the corresponding cyclic trimer **7** (11%).[7] No other higher oligomers were isolated. The success of Na_2S/Al_2O_3 in closing the twenty-membered ring of **3**, albeit in somewhat lower yield than the for the twelve-membered ring of **1** (55-65%),[5] augurs well for application to the synthesis of other expanded cyclophanes, particularly in light of the recently reported failure of $Na_2S{\cdot}9H_2O$ to close a triply bridged relative of **2**.[8]

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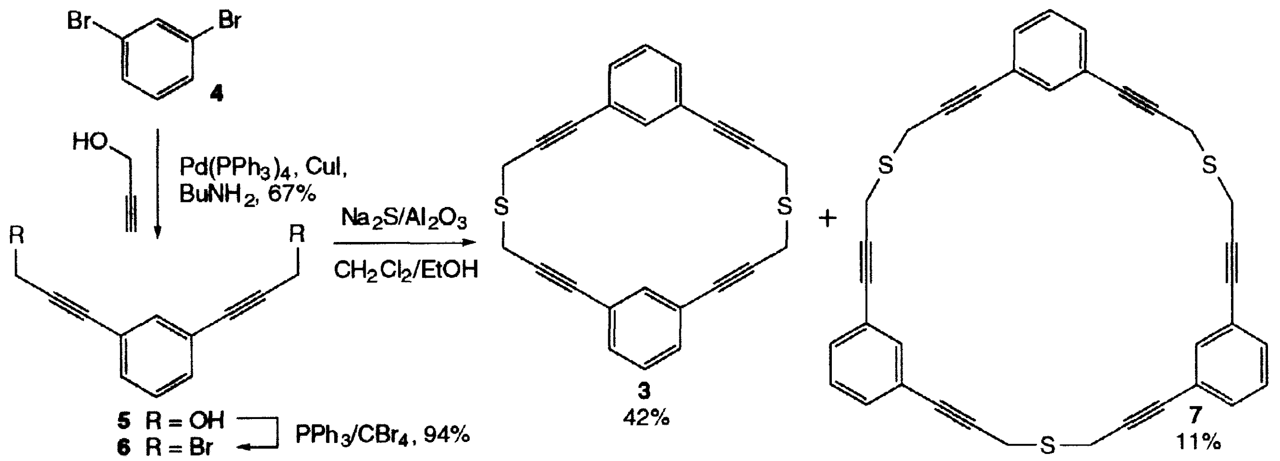
PII: S0040-4039(98)00233-0



Scheme 2.

The substantial increase in the size of the internal cavity that accompanies expansion of **1** to **3** brings with it considerable changes in the nature of the cyclophane system. For a start, a single crystal X-ray structure determination of **3**[9] revealed that it had crystallized in what may be described as a twisted *anti* conformation (Figure 1). There are many documented examples of *anti*-2,11-dithia[3.3]metacyclophanes[3] and, to the best of our knowledge, this conformation is without precedent.[10] This is not surprising, since the corresponding conformation in an *anti*-2,11-dithia[3.3]metacyclophane series would suffer from severe intramolecular steric interactions between the two internal hydrogen atoms. As might be expected, the aromatic rings and the sp-hybridized carbon atoms bonded directly to them show no significant deviations from planarity. On the other hand, a somewhat unexpected feature of the structure is that the alkyne units are distorted from linearity towards the molecular cavity. The least distorted is the C(14)-C(15) triple bond, the attached bonds of which are bent by 0.2 and 2.0° (θ in Figure 1). The most distorted is the C(19)-C(20) alkyne, which exhibits bend angles of 5.6 and 6.0°. The average bend angle is 3.0°. The origin of these distortions and, perhaps to some extent, the unexpected conformation may be the minimization of space in the cavity of the macrocyclic framework of **3**. The remaining bond angles and lengths are within normal ranges: the sp-sp^2 bonds average 1.442 Å, the sp-sp^3 bonds average 1.455 Å and the C-S bonds average 1.814 Å. No noteworthy intermolecular contacts are evident.

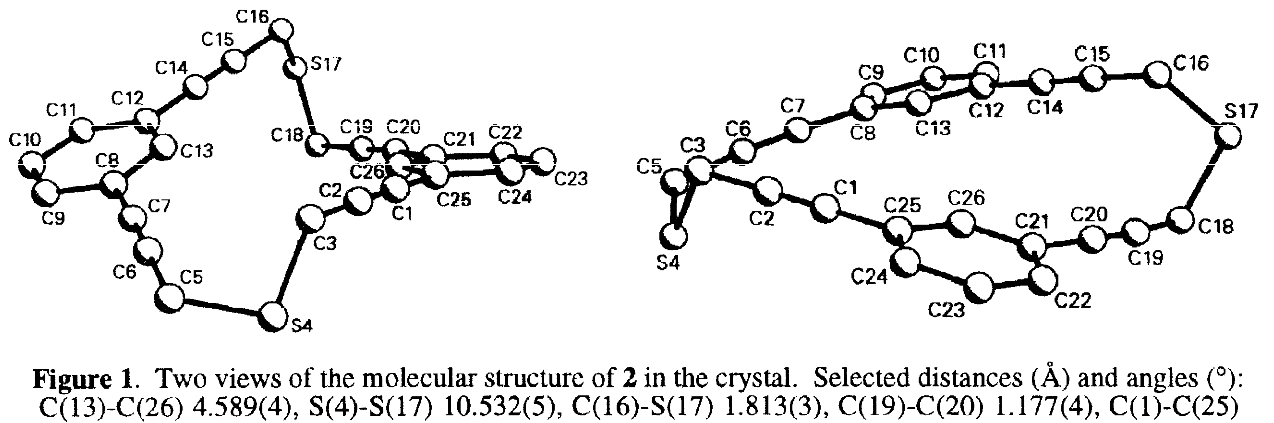


Figure 1. Two views of the molecular structure of **2** in the crystal. Selected distances (Å) and angles (°): C(13)-C(26) 4.589(4), S(4)-S(17) 10.532(5), C(16)-S(17) 1.813(3), C(19)-C(20) 1.177(4), C(1)-C(25) 1.444(4), C(2)-C(3) 1.455(4); C(3)-S(4)-C(5) 101.0, C(12)-C(14)-C-(15) 179.8(3), C(14)-C(15)-C(16) 178.0(4), C(18)-C(19)-C(20) 174.0, C(19)-C(20)-C(21) 174.4, C(15)-C(16)-C(17) 115.2(2).

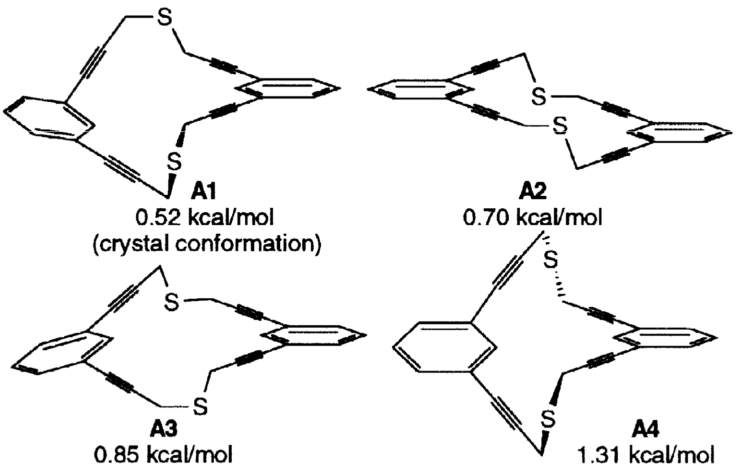


Figure 2.
Calculated *anti* conformers for **3**.
Energies given are those above the global minimum.

In order to obtain more information about possible solution structures, a conformer search allowing for rotation about all of the non-acetylenic bridge bonds was performed on **3** using the Spartan software package at the AM1 level. Seven conformers within 10 kcal of the global minimum were identified and all of these were calculated to be within 1.31 kcal/mol in energy of each other. The three lowest energy conformers were *syn* conformers with the *chair,boat* (0.00 kcal/mol), *chair,chair* (0.01 kcal/mol) and *boat,boat* (0.14 kcal/mol) arrangements of the bridges.[3,11,12] The remaining conformers were the *anti* conformers shown in Figure 2. The conformer observed in the solid state **A1** was calculated to be the lowest energy of these, 0.52 kcal/mol above the global minimum. Conformers **A1**, **A3** and **A4** are all unprecedented twisted *anti* conformers, whereas **A2** is akin to one proposed[13] and observed[10b] for known *anti*-2,11-dithia[3.3]metacyclophanes.

The bridge protons of **3** appear as a sharp singlet at δ 3.70 in the ^1H nmr spectrum and no line broadening is observed at -90 °C. This is consistent with a rapid exchange in the environments of the two diastereotopic protons on each of the bridge methylene groups *via* a *syn/syn'* and/or *anti/anti'* conformational interconversion. An accidental chemical shift degeneracy may also be in effect. There is no reason to suspect that **3** exists as anything other than a rapidly equilibrating mixture of conformers, even at low temperature.

Because of the significantly greater distance between the two aromatic rings of **3** (C(13)-C(26) = 4.59 Å) compared to those of *syn*-**1** (distance between internal C atoms = 3.05 Å),[11] the chemical shifts of the internal aromatic protons of **3** might not be expected to provide much meaningful information regarding the conformation in solution. In fact, these appear at δ 7.60, slightly downfield from those of its precursors **5** (δ 7.50) and **6** (δ 7.52). Any significance attributed to this small downfield shift should be weighed against the observation that the internal protons of **7** also appear at δ 7.60.

In summary, an expedient route to the first of a family of expanded cyclophanes has been developed. Work aimed at the conversion of **3** into other expanded metacyclophanes as well as the synthesis of other types of expanded cyclophanes is now in progress.

Acknowledgements: The authors gratefully acknowledge financial support of this work from the Natural Sciences and Engineering Research Council (NSERC) of Canada.

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6. *Experimental procedure for 3.* To a well-stirred mixture of dibromide **6** (600 mg, 1.92 mmol), CH_2Cl_2 (1000 ml) and ethanol (100 ml) under nitrogen was added Na_2S/Al_2O_3[5] (2.64 mmol/g, 1.60g, 4.23 mmol) in eight equal portions at 30 min intervals. Tlc analysis indicated that the reaction was complete 6 h after the first addition of the reagent. The mixture was filtered and the solvents were removed under reduced pressure. The residue was chromatographed on silica (3:2 hexanes/CH_2Cl_2) to afford first **3** (R_f = 0.33, 147 mg, 42%) and then **7** (R_f = 0.26, 40 mg, 11%).
7 **3**: mp 224-226 °C; δ_H ($CDCl_3$, 300 MHz) = 7.60 (2H, apparent t, J = 1.5 Hz), 7.29 (4H, m), 7.16 (2H, m), 3.70 (8H, s); δ_C ($CDCl_3$, 75 MHz) = 135.8, 130.9, 128.2, 123.3, 85.7, 83.2, 21.1; MS (EI, 70 eV) m/z (%) = 368 (36, M^+), 333 (23), 277 (20), 276 (25), 264 (21), 152 (35), 151 (41), 150 (29), 140 (22), 139 (100), 126 (29); IR (nujol) C≡C not observed; Calcd. C 78.22, H 4.38; Found C 78.33, H 4.28. **7**: mp 158-161 °C; δ_H ($CDCl_3$, 300 MHz) = 7.60 (3H, br s), 7.37 (6H, m), 7.25 (3H, m), 3.70 (12H, s); δ_C ($CDCl_3$, 75 MHz) = 135.3, 131.4, 128.3, 123.1, 85.2, 82.5, 19.9; MS = M^+ not observed using EI, CI, FAB, electrospray. Tentative assignment as the trimer is based on analogy to related reactions.[5] IR (nujol) C≡C not observed; Calcd. C 78.22, H 4.38; Found C 77.95, H 4.38.
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9. Crystal data for **3**: colorless irregular crystal (0.30 x 0.30 x 0.15 mm) from heptane/EtOAc. $C_{24}H_{16}S_2$, M = 368.51, triclinic, $P\bar{1}$ (#2), Z = 2, a = 10.868 (6), b = 11.315 (3), c = 8.748 (6) Å, α = 91.66 (3), β = 112.27 (4), γ = 106.32 (3) °, V = 944.2 (9) Å^3, D_c = 1.296 g cm^{-3}, F(000) = 384, μ (Mo-K_α) = 2.73 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer with graphite monochromated Mo-K_α radiation (λ = 0.71069 Å), ω–2θ scan type with ω scan width = 1.37 + 0.35 tanθ, ω scan speed 4.0 ° min^{-1} (up to three rescans for weak reflections), 3542 reflections, 3352 unique (R_{int} = 0.013), empirical absorption correction (max., min. corrections = 1.00, 0.95, secondary extinction correction (coefficient = 0.96542 10^{-6}), giving 2192 with $I > 2\sigma(I)$. Solution and refinement by direct methods using the TEXSAN package of the Molecular Structure Corporation; all non-H atoms refined anisotropically; full matrix least squares refinement with 236 variable parameters led to R = 0.041, R_w = 0.035, GOF 1.73.
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