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Restriction of the Inversion Process of the 1,3-Bridged Ring in the Rigid Conformer of 24-Methyl-2,17-Dithia[3.3](2,2')Biphenyleno(1,3)Cyclophane

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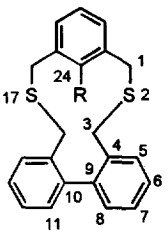
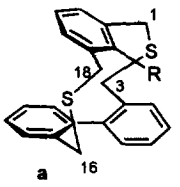
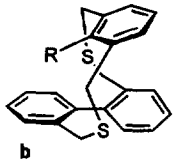
Abstract: The title compound **3** was prepared via a cyclization reaction between two known precursors. It is confirmed that the inversion process of the 1,3-bridged ring in the 2,17-dithia[3.3](2,2')biphenyleno(1,3)cyclophane system was restricted with a conformational energy barrier of >84 kJ mol^{-1}. The adopted rigid conformation is represented by **3a** (or **3b**) having the methyl protons located above the cavity of one of the benzene rings. This is consistent with the preferred conformation derived from semiempirical molecular orbital PM3 calculations. All the protons in this rigid conformer could be assigned by its COSY spectra and results from a series of NOE experiments. © 1997 Published by Elsevier Science Ltd.

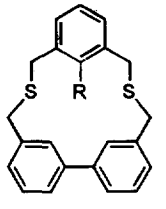
The family of cyclophanes with a biphenyl unit in the molecular structure is small but many of its members exhibit novel conformational behavior.[1-3] The dithiabiphenylenophane **1** was initially reported[2] to be chiral and a rigid conformation **1a** (or **1b**)was suggested.[2,3] Results from variable-temperature ^{1}H NMR studies[3] of **1**, **2** and related biphenylenophanes supported an inversion process of the 1,3-bridged ring at room temperature as represented by an equilibrium between **1a** and **1b** (or **2a** and **2b**) which, however, could not be restricted even at -90 °C. Replacing the hydrogen at C-24 in **1** with a methyl group as in **3** is expected to increase the conformational barrier significantly. Although the synthesis of the dithiacyclophanes **5**[1a] and **6**[1b] has been reported there was, however, no mention of their conformational behaviour. Thus whether the inversion process between **3a** and **3b** could be restricted, hence the spectroscopic evidence for a rigid conformation **3a** (or **3b**), is of special interest.







1, R = H ; **2**, R = F ; **3**, R = CH_3



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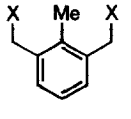
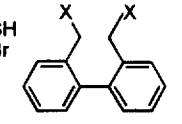
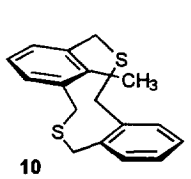


6, X = SH
7, X = Br



8, X = Br
9, X = SH

2,2'-Bis(mercaptomethyl)toluene (**6**)[4] was coupled with 1,3-bis(bromomethyl)biphenyl (**8**)[5] in the presence of a base under high dilution conditions[6] to give the desired dithiacyclophane **3** in only 17% yield. This could be a result of unfavourable steric interactions as the disulphide of **6** approached the dibromide **8**. This is clearly supported by the fact that a similar cyclization reaction between compounds **7**[4] and **9**[7] under similar conditions afforded the dithiacyclophane **3**[8] in 47% yield. In the mass spectrum of **3**, only a weak molecular ion at *m/z* 362 was observed with the base peak at *m/z* 211 indicating a ready but unsymmetrical fragmentation involving the cleavage of two of the C-S bonds.



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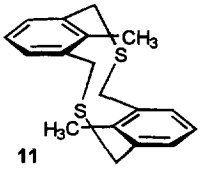

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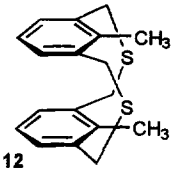

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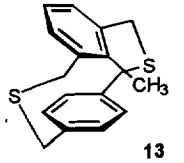

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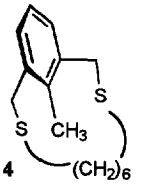


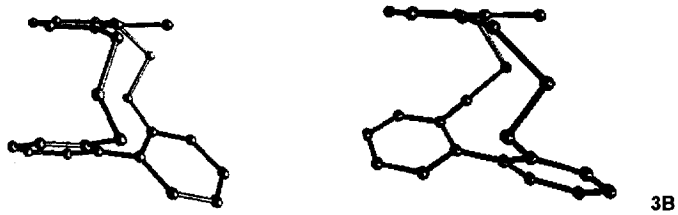
14

Compound **3** exhibits axial chirality in the biaryl moiety. In either **3a** or **3b** each of the four pairs of methylene protons is diastereotopic. In an inversion of the 1,3-bridged ring in **3**, **3a** is converted to **3b** which is in fact equivalent to **3a**. In such a process, however, the two pairs of methylene protons at C1 and C18 are exchanged although each pair remains diastereotopic. A similar phenomenon applies to the two pairs of methylene protons at C3 and C16. The above should then result in two averaged AB systems. The ^{1}H NMR (500 MHz) spectrum of **3** shows four sets of AB quartets for the methylene protons indicating that each pair of methylene protons are magnetically non-equivalent (diastereotopic) with no exchange processes. This is thus consistent with a rigid conformation for **3**. All eight protons in the two benzene rings of the biphenyl moiety are also well resolved and appear as four sets of triplets for H-6,7,12,13 and four sets of doublets for H-5,8,11,14, respectively. Based on the ^{1}H-^{1}H COSY spectrum (in $CDCl_3$) and a series of NOE difference experiments (in $C_6D_5NO_2$), the dithiacyclophane **3** is believed to adopt the conformation represented by **3a** (or **3b**). Results from our semiempirical molecular orbital PM3[9] calculations (also optimizing the most stable conformation for the C-S-C bridges) suggest that the two most preferred conformations of **3** are **3A** and **3B** (Figure 1) with the former being about 13 kJ mol^{-1} more stable. This is clearly consistent with our qualitative prediction for the preference of **3a**. The location of the methyl protons above the cavity of one of the biphenyl rings in **3a** results in a significantly shielded singlet at δ1.62 (in $CDCl_3$; δ1.40 in $C_6D_5NO_2$). This is less shielded compared to protons in the more closely stacked dithiacyclophanes **10** (δCH_3 = 1.30)[1b] and **11** (δCH_3 = 1.30)[5] but shifts appreciably from chemical shifts of methyl protons in **12** (δCH_3 = 2.51)[5] and **13** (δCH_3 = 1.90),[10] respectively.

Through the long range couplings observed (in $CDCl_3$) between the methyl protons and the doublets at δ7.15 and δ7.07, and the triplet at δ6.83 (H21). In addition, from the COSY spectrum, two sets

of coupled systems are observed in the aromatic region between signals at δ7.98 and δ7.42, and δ7.24 and δ7.01. Another is between signals at δ7.59 and δ7.24, and δ7.04 and δ6.83.

Assignment of the protons In **3a** (**3A**; Figure 1) is a challenge. The following discussion is based on the COSY spectrum and/or several NOE experiments determined using $C_6D_5NO_2$ as the solvent (Table 1). One of the methylene protons at C3 is located in the shielding zones of the two stacking benzene rings. This is assigned to the significantly shielded (compared to chemical shifts of other methylene protons; Table 1) H3 at δ2.73 (hence H3' by COSY). Irradiation at H3 led to enhancement of the signals at δ3.41 (H3'), 6.80 (H11) and 7.15 (H22). Thus H12,13,14 and H20 could be assigned, respectively, based on the correlated connectivity by COSY. When H20 and H22 were irradiated in separate experiments, H18' (hence H18 by COSY) and H1' (hence H1 by COSY) could be assigned on the basis of their NOE enhancements. Saturation of H14 resulted in an enhancement of the signal at δ7.98 assigned to H16' (hence H16 by COSY). When H16 was irradiated, enhancement was observed for signals at δ1.40 (CH_3), 3.70 (H16') and 6.96 which is assigned to H8. Hence H5,6,7 could be assigned, respectively, based on the correlated connectivity by COSY.



3A **3B**

Figure 1. Optimized conformations **3A** and **3B** derived from semiempirical molecular orbital calculations.

Table 1. ^{1}H NMR (500 MHz) chemical shifts for protons in dithiacyclophane **3**.

Solvent	Methylene and Methyl Protons								
	H-1	H-1'	H-18	H-18'	H3	H3'	H16	H16'	CH_3
$CDCl_3$	3.47[a,c]	3.89[b,c]	3.52[a,d]	4.06[b,d]	2.76[a,e]	3.41[b,e]	3.11[a,f]	3.79[b,f]	1.62
$C_6D_5NO_2$	3.34	3.77	3.41	3.90	2.73	3.32	3.03	3.70	1.40

Solvent	Aromatic Protons										
	H-5	H-14	H-6	H-13	H-7	H-12	H-8	H-11	H-20	H-22	H-21
$CDCl_3$	7.98[g,h]	7.59[g,h]	7.42[i,j]	7.20[i,j]	7.24[k,h]	7.04[k,h]	7.01[l,j]	6.80[l,j]	7.07[g,h]	7.15[g,h]	6.83[k,h]
$C_6D_5NO_2$	7.96	7.56	7.45	7.17	7.31	7.03	6.96	6.76	6.99	7.05	6.69

a: δ_A of an AB quartet. b: δ_B of an AB quartet. c: *J* 13.7 Hz. d: *J* 13.3 Hz.
e: *J* 16.3 Hz. f: *J* 17.1 Hz. g: a doublet. h: *J* 7.6 Hz.
i: a doublet of a triplet. j: *J* 7.6, 1.2 Hz. k: a triplet. l: a doublet of a doublet.

The above ^{1}H NMR data clearly show that dithiacyclophane **3a** (**3b**) is conformationally rigid at room temperature. In the high-temperature ^{1}H NMR measurements carried out between 24 °C and 130 °C, the chemical shifts of the four AB quartets corresponding to the four pairs of methylene protons remained

practically unchanged. This corresponds to a conformational energy barrier of >84 kJ mol^{-1} based on approximations using the coalescence temperature method.[11] The dithiacyclophane **3** is thus significantly more rigid than the related systems **1** and **2**.[3] The high energy barrier is, however, consistent with that (>95 kJ mol^{-1}) observed for the conformational barrier for ring flipping in dithia[10](3)cyclophane **14**.[1b] It is worth noting that in the variable-temperature ^{1}H NMR studies, the change in the chemical shift of the methyl protons was relatively more significant as compared to those of the methylene signals. This was not unexpected as the methyl protons are projected into the cavity of one of the benzene rings (**3a** or **3b**). As the shielding effect is more sensitive to the relative position of a proton in space, a small change in the conformation of **3b** (**3c**) due to a change in temperature, and thus the averaged position of the methyl protons relative to the benzene ring concerned, may induce an appreciable shift in the methyl signal.

We have thus confirmed that the inversion process of the 1,3-bridged ring in a 2,17-dithia[3.3](2,2')biphenyleno(1,3)cyclophane system, represented by an equilibrium between **1a** and **1b** (or **2a** and **2b**) but was previously in doubt, could be restricted by an appropriate substitution at C24. The adopted rigid conformation is represented by **3a** (or **3b**) having the methyl protons projected into the cavity of one of the benzene rings.

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