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Synthesis of Dithia[3.3]biphenyleno(2,2')(1,2)-, (1,3)-, (1,4)cyclophanes and Their Atropisomerism and Dynamic Stereochemistry

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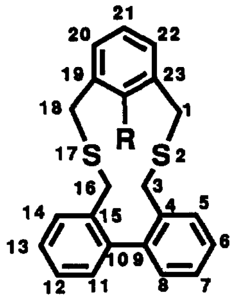
Abstract: The dithiacyclophanes (1), (2), (3) and (4) were prepared by intermolecular cyclization reactions under high dilution conditions Detailed ^{1}H NMR spectroscopic analyses and dynamic NMR studies have indicated that pseudo-rotation of the biphenyl unit is restricted up to a temperature of 443K in (1), (2) and (3) involving energy barriers estimated to be >75 kJ mol^{-1} At room temperature, a flipping process of the 1,3-bridged ring in (1) and (2) is however clearly evident based on analyses of the aromatic protons in the 1D and 2D ^{1}H NMR spectra. The dithiacyclophane (4) proves to be conformationally the most mobile among the three members and exhibits two-step conformational processes involving first an inversion process of the 1,2-bridged ring followed by a pseudo-rotation (racemization) of the biphenyl moiety, with an estimated free energy of activation of 61.9 kJ mol^{-1}, at high temperatures

Whereas extensive work has been directed toward the studies of condensed benzenoid cyclophanes,[1] cyclophanes derived from the biphenyl system have received less attention Several biphenylenophane systems however have been employed successfully as precursors to novel aromatic benzenoid compounds[2-6] while others exhibit interesting conformational behvaior.[7-10] The dithiabiphenylenophane (1) was earlier reported[11] to be chiral, the two sets of methylene protons appeared as two AB systems which remained so independent of temperature up to 150°C This result may be consistent with either a rigid pseudo-*syn* conformation (**1a**) or an equilibrium among conformers with a rigid biphenyl moiety and a mobile 1,3-bridged ring. Results from dynamic ^{1}H NMR spectroscopic studies of cyclophanes (**5**)[7] and (**6**)[8,9] however have shown that these systems are conformationally mobile Molecular models of (**1**) also suggest possible ring flipping of the 1,3-bridged ring although the pseudo-rotation of the biphenyl moiety might involve a larger energy barrier The above observation has prompted us to reinvestigate the conformational behavior of (**1**) The fluoro derivative (**2**), the related 1,4-bridged and 1,2-bridged systems (**3**) and (**4**) were also prepared to allow a more comprehensive comparative study.

Intramolecular coupling reactions of 2,2'-bis(mercaptomethyl)biphenyl (**7**)[11] with (**8**),[12] (**9**), (**10**) and (**11**) respectively under high dilution conditions[13] gave the desired dithiabiphenylenocyclophanes (**1**) - (**4**) in 42, 51, 51 and 62% yield. In their respective EI mass spectra, only a moderate or weak molecular ion was observed but the various fragmentation processes involving cleavage of C-S bonds were very similar among all four dithiacyclophanes (**1**) - (**4**) The melting point (123-127°C) of a sample of (**1**) obtained in our work was significantly lower than that (147-155°C) reported.[11] A molecular ion observed at *m/z* 349 (M+1) in the CI mass spectrum of our sample and a satisfactory microanalytical analysis however helped to confirm the structure of **(1)**. The respective structures **(1)** - **(4)** are also well supported by the ^1H NMR spectral data (Table 1).



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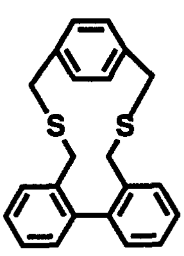
(2) R = F



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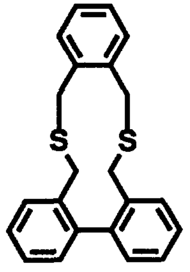

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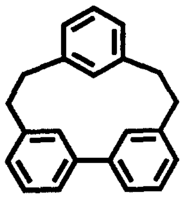

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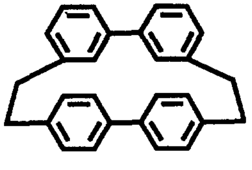

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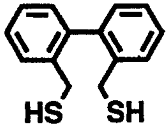

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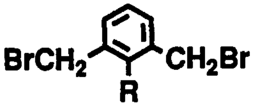


(8) R = H
(9) R = F

(10)

(11)

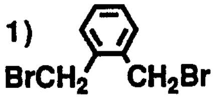


Table 1. Product Yields and ^1H NMR (300 MHz) Chemical Shifts for Dithiacyclophanes (1) - (4).

	Yield	Methylene Protons		Aromatic Protons						
Cpd	%	C(1,18)H$_2$	C(3,16)H$_2$	H5,14	H6,13	H7,12	H8,11	H24	H20,22	H21
(1)	42	3 46^{a,c} 3 55^{b,c}	3 10^{a,d} 3 73^{b,d}	7 74^{e,g}	7 36^{f,g}	7 21^{f,g}	6 99^{e,g}	6 30^{h}	7 13^{h}	
(2)	51	3 64^{h}	3.15^{a,i} 3 70^{b,i}	7 79^{j,g}	7 34^{k,l}	7 18^{f,g}	6 97^{l,m}	---	7 14^{f,n}	6 89^{f,o}
(3)	51	3.31,^{a,p} 3.53^{b,p}		7.2-7.4^{q}						
(4)	62	3 30,^{a,r} 3.48^{b,r}		7 3-7 4^{q}						

$^a\delta_A$ of an AB quartet. $^b\delta_B$ of an AB quartet. ^cJ = 13 8 Hz ^dJ = 16 7 Hz ^{e}A doublet. ^{f}A triplet. ^gJ = 7 5 Hz ^{h}A singlet. ^iJ = 17 1 Hz ^{j}A doublet ^{k}A double triplet. ^lJ = 1.2, 7 5 Hz. ^{m}A double doublet. ^nJ = 7 3 Hz ^oJ = 7 6 Hz ^pJ = 12 6 Hz ^{q}A multiplet. ^rJ = 12.7 Hz

For all four dithiacyclophanes **(1)** - **(4)** the methylene protons are diastereotopic if the biphenyl moiety is conformationally rigid, even when the 1,3-bridged ring undergoes flipping in **(1)** [**(1b)** ⇌ **(1c)**] or **(2)** [**(2a)** ⇌ **(2b)**], the 1,4-bridged ring undergoes free rotation in **(3)** [**(3a)**] and the 1,2-bridged ring undergoes ring inversion in (4) [(4a) $\rightleftharpoons$ (4b)]. Each pair of methylene protons are thus magnetically non-equivalent and expected to appear as an AB quartet in the region of δ3.0-4.0 (Table 1) In principle each of (1) - (4) would have two sets of AB quartets but only (1) behaves as expected. One set of methylene protons in (2) in fact appear as a singlet at δ 3.64. Diastereotopic AB protons of methylene groups of the CH_2SCH_2 bridge(s) in several thia- and dithiacyclophanes have however been reported to exhibit identical chemical shifts.[14,15] On the other hand, the two sets of AB quartets in each of (3) and (4) presumably have identical chemical shifts and thus are unresolved. Similar phenomena were also observed[15,16] in other related cyclophane systems. The aromatic protons of (3) and (4) appear as multiplets and are not sufficiently well-resolved. Those of (1) and (2) however could be assigned respectively which in fact help in confirming their conformational behavior (see later discussion)

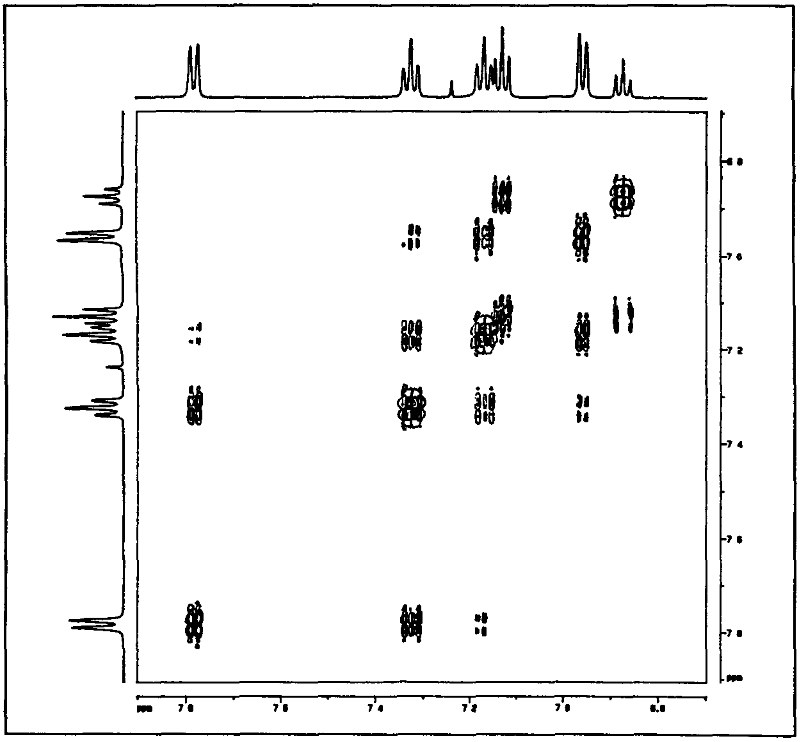
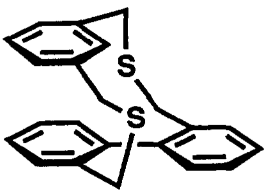


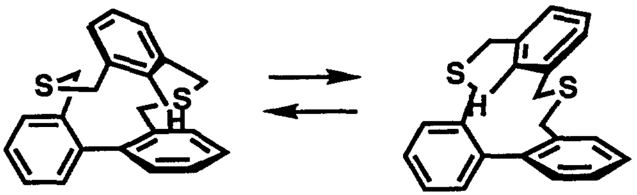
Figure 1. COSY ^1H NMR spectrum ($CDCl_3$; 500 MHz) of dithiacyclophane (2)

All eight protons in the two benzene rings of the biphenyl moiety in a rigid conformation such as (1a) or (2a) would be expected to be magnetically non-equivalent and result in complex multiple coupling patterns. The ^1H NMR spectrum of (1) and (2) (Table 1) however shows well-resolved simple splitting patterns more consistent with averaged signals resulting from rapid interconversion processes (1b) $\rightleftharpoons$ (1c) and (2a) $\rightleftharpoons$ (2b) respectively within the NMR time scale. Based on the ^1H NMR spectra (300 MHz) obtained from a series of decoupling experiments using a sample of (**1**), *ortho* couplings were evidently observed between signals at δ 7.74 and 7.36, and δ 7.21 and 6.99. The expected deshielding of H5,14 by the anisotropic effect of sulfur due their close proximities helps assign the doublet at δ 7.74 to H5,14. On the other hand H8,11 are slightly shielded by the respective adjacent benzene rings in the biphenyl moiety and correspond to the doublet at δ 6.99. Thus the other signals could be assigned to H6,13 and H7,12 respectively (Table 1). The above assignments are well supported by the COSY spectrum (500 MHz) of (**2**) (Figure 1) showing the respective couplings among H5-8,11-14. In fact the respective chemical shifts of these aryl protons in both (**1**) and (**2**) are very similar (Table 1).

The projection of H24 into the cavity of one of the biphenyl rings in (**1**) results in the significantly shielded singlet at δ 6.30. H20-22 in (**1**) are however unresolved and appear as a broad singlet at δ 7.13. With the introduction of fluorine at C24 in (**2**), H21 being *para* to fluorine is shifted about 0.25 ppm upfield as expected. H-F couplings (J = 7.3 Hz) between H20,22, which appear as a triplet at δ 7.14, and fluorine are clearly evident (Figure 1). Assignments of the bridging methylene protons are based on a COSY spectrum of (**2**). Long-range couplings are observed between the singlet at δ 3.64 [C(1,18)H_2] and the triplet at δ 7.14 (H20,22), and one doublet of the AB at δ 3.15 [C(3,16)H_2] and the doublet at δ 7.79 (H5,14). By analogy, the methylene protons in (**1**) could thus be assigned (Table 1).



(1a)



(1b) **(1c)**

When a sample of (**1**) was cooled from 283K to 183K, only slight broadening of the two AB quartets were observed but more significant changes were noted in the $\Delta\delta$ (δ_B - δ_A) values (Figure 2b). Apparently the conformational barrier to ring flipping in (**1b**) ⇌ (**1c**) is very low without resulting in a frozen conformation such as (**1b**) or (**1c**) within the temperature range studied. The change in $\Delta\delta$ could be due to a combination of solvent shift effect and a change in the rate of flipping of the 1,3-bridged ring leading to a change in the chemical shifts of the methylene protons. Similar phenomena have been observed in other dithiacyclophanes.[17] In the high-temperature study (Figure 2a) between 308K and 443K, chemical shifts of the two AB quartets and their respective $\Delta\delta$ values remained practically unchanged. This is consistent with restricted pseudo-rotation in the biphenyl moiety with an energy barrier estimated[18] at >90 kJ mol^{-1}. The transition state (**12**) in the pseudo-rotation in (**1**) involves a planar biphenyl moiety. Molecular models of (**12**) of (**1**) indicates severe angle strains (large angle β) and steric strains between H8 and H11 due partly to the geometric demand of the 1,3-bridged ring The high energy barrier to pseudo-rotation in (1) is not unexpected as racemization studies[19-21] of some optically active 2,2'-bridged biphenyl systems gave the free energy of activation in the range of 85-105 kJ mol^{-1} The fluoro derivative (2) behaved very similarly in the high-temperature dynamic ^{1}H NMR study. No sign of coalescence of the AB quartet was observed up to 423K corresponding to an energy barrier of >80 kJ mol^{-1}

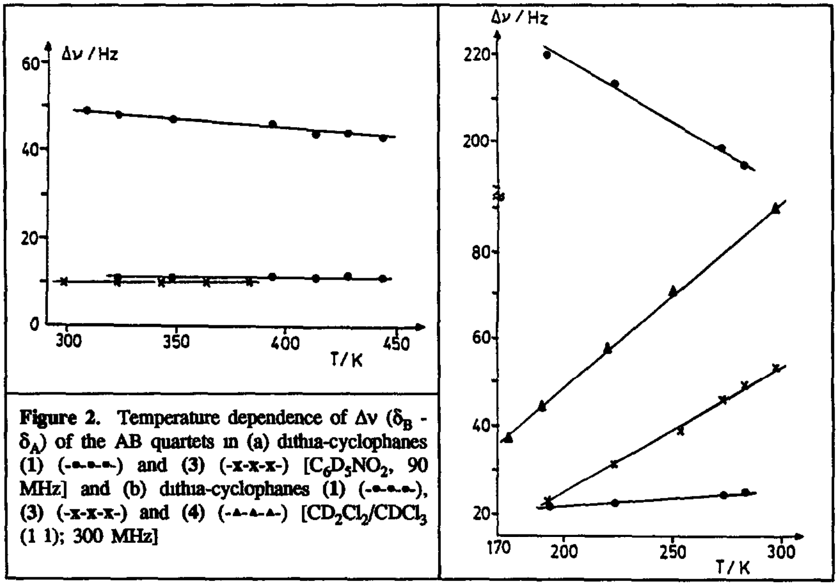
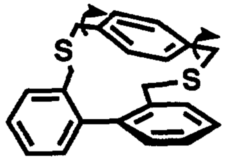
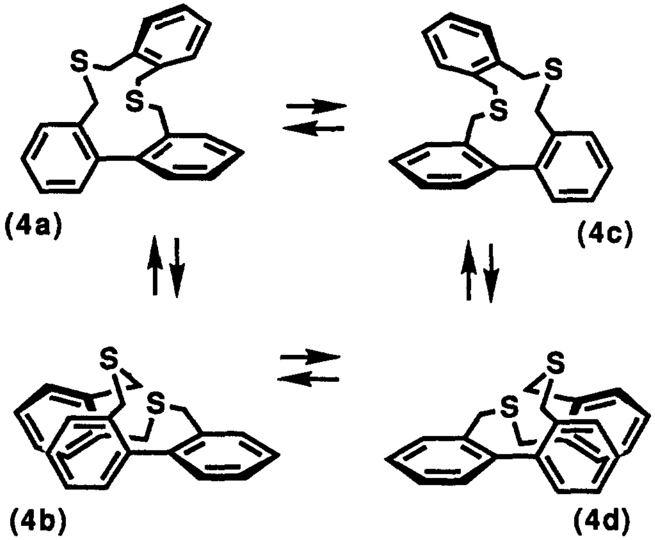


Figure 2. Temperature dependence of Δν (δ_B - δ_A) of the AB quartets in (a) dithia-cyclophanes (1) (-•-•-•-) and (3) (-x-x-x-) [$C_6D_5NO_2$, 90 MHz] and (b) dithia-cyclophanes (1) (-•-•-•-), (3) (-x-x-x-) and (4) (-▲-▲-▲-) [$CD_2Cl_2/CDCl_3$ (1:1); 300 MHz]

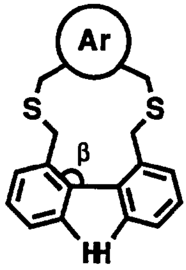
Results from the conformational study of (3) are also similar to those described for (1). The Δδ of the AB quartet which did not coalesce remained practically constant between 298K and 383K (Figure 2a), suggesting an energy barrier of >75 kJ mol^{-1} for the pseudo-rotation of the biphenyl moiety in (2). In fact molecular models of (12) of (3) indicate even larger angle and steric strains due to the geometric demand of the 1,4-bridged ring In the low-temperature study (Figure 2b) however the Δδ values changed significantly This could again be due to a solvent shift effect and a change in rate of rotation or tilting of the 1,4-bridged ring

Molecular models of (12) of the dithiacyclophane (4) indicate the least angle and steric strains among all three members due to the more flexible 12-membered macrocycle in (4). Inversion of the 1,2-bridged ring [(4a) ⇌ (4b)] is expected to proceed freely and thus it was no surprise that no frozen conformer of (4) could be observed in the low-temperature study, although the change in Δδ values within the temperature range of 297K and 173K (Figure 2b) is the most significant among all three dithiacyclophanes studied. As a sample of (4) in $C_6D_5NO_2$ was warmed from 298K to 351K, the AB quartet (δ_A = 3.24, δ_B = 3 34) broadened and eventually coalesced at 316K (T_c) At 351K a sharp singlet was observed at the averaged position (δ3.30) of the initial AB quartet. This is consistent with an additional conformational process involving a rapid interconversion **(4a)** ⇌ **(4c)** [**(4b)** ⇌ **(4d)**] due to pseudo-rotation in the biphenyl moiety. When both the processes **(4a)** ⇌ **(4b)** [**(4c)** ⇌ **(4d)**] and **(4a)** ⇌ **(4c)** [**(4b)** ⇌ **(4d)**] are fast within the NMR time scale, each pair of the two sets of AB methylene protons become enantiotopic or magnetically equivalent and thus appear as an averaged sharp singlet. An estimate of the energy barrier for the interconversion process **(4a)** ⇌ **(4c)** [**(4b)** ⇌ **(4d)**] could be obtained from the coalescence temperature (T_c) method.[18] As shown in Figure 2a, there is no significant dependence of the frequency separation (Δν) of the AB quartets on temperature in the high temperature studies of **(1)** and **(3)**. Thus the chemical shift difference (Δν) at T_c (316K) in the dynamic NMR study of **(4)** was assumed to be very similar to that at 298K (Δν = 58.2 Hz) The transition state free energy at coalescence, $\Delta G^{\ddagger}_c$, could then be estimated from the equation: $\Delta G^{\ddagger}_c = 0.019 T_c(9.972 + \log T_c / k_c)$ kJ mol^{-1}, where k_c (rate constant for the exchange at T_c) = $\pi/\sqrt{2}\,(\Delta\nu^2 + 6J^2)^{1/2}$ The $\Delta G^{\ddagger}_c$ value (an estimate of the conformational barrier) for **(4a)** ⇌ **(4c)** [**(4b)** ⇌ **(4d)**] is thus calculated to be 61.9 kJ mol^{-1} — a value similar to the range of 40-75 kJ mol^{-1} reported[22,23] for the energy barriers to inversion of conformation in several simple 2,2'-bridged biphenyl systems


(3a)



(4a) **(4c)** **(4b)** **(4d)**



(12)

Our observation has indicated that the conformational behavior of both **(1)**, **(2)** and **(3)** do not involve pseudo-rotation in the biphenyl moiety. Based on the detailed ^{1}H NMR spectroscopic analyses of the aromatic protons, **(1)** and **(2)** clearly undergo the resepctive flipping processes **(1b)** ⇌ **(1c)** and **(2b)** ⇌ **(2c)** of the 1,3-bridged rings instead of adopting rigid conformations **(1a)** and **(2a)**. The dithiacyclophane **(4)** was found to be conformationally the most mobile and exhibits the two-step conformational processes of **(4a)** ⇌ **(4b)** [**(4c)** ⇌ **(4d)**] and **(4a)** ⇌ **(4c)** [**(4b)** ⇌ **(4d)**] respectively

Experimental Section

All melting points were determined on a Synbron/Thermolyne MP-12615 melting apparatus and are uncorrected. The 1D ^{1}H NMR spectra were determined in $CDCl_3$, $CDCl_3/CD_2Cl_2$ (1·1) [for low-temperature studies] or $C_6D_5NO_2$ [for high-temperature studies] on a Bruker ACF-300 (300 MHz) or a JEOL FX90Q (90 MHz) Fourier transform spectrometer. The 2D ^{1}H NMR spectra were determined in $CDCl_3$ on a Bruker AMX-500 (500 MHz) and collected with 4K x 1K data points All chemical shifts are reported in ppm downfield from tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer. Mass spectra were determined using electron impact (EI) on a VG Micromass 7305 mass spectrometer at 70 eV or chemical ionization (CI) on a Hewlett Packard 5988A mass spectrometer. Relative intensities are given in parentheses. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, National University of Singapore.

General procedure for the coupling reactions. A solution of 2,2'-bis(mercaptomethyl)-biphenyl (7)[11] (0.50 g, 2 0 mmol) and the respective bis(bromomethyl)-compound (0.54 g, 2.0 mmol) in benzene (250 mL) was added dropwise over a period of 5-8 h into a well-stirred solution of KOH (0.23 g, 4.0 mmol) in nitrogen-purged 95% ethanol (1 L) After the addition, the mixture was further stirred for 15 h and the bulk of the solvent was then removed under reduced pressure. The residue was extracted with dichloromethane The organic layer was washed with water, dried, and evaporated. The crude product was chromatographed on silica gel with dichloromethane/hexane (1 1) as eluant.

2,17-Dithia[3.3]biphenyleno(2,2')(1,3)cyclophane (1) The product (**1**) (0.29 g, 42%) was prepared from (**7**) and (**8**) as described in the general procedure Recrystallization from benzene/hexane gave colorless crystals of (**1**), m.p. 123-127°C (lit.[11] 147-155°C) MS/EI ($M^{\cdot+}$) *m/z* 348 (6%), 211 (81), 179 (100), 178 (83), 165 (35). 135 (17), 104 (27), MS/CI (methane) *m/z* 349 (M+1, 100%), 213 (20), ^{1}H NMR (300 MHz), see Table 1, IR (KBr) 1440, 1230, 1195, 1100, 1050, 1009, 956, 905, 840, 806, 762, 732, 718 cm $^{-1}$. Calcd for $C_{22}H_{20}S_2$ C, 75 82, H, 5 78%. Found C, 76 18; H, 5.51%

24-Fluoro-2,17-dithia[3.3]biphenyleno(2,2')(1,4)cyclophane (2) The product (**2**) (0.38 g, 51%) was prepared from (**7**) and (**9**) as described in the general procedure Recrystallization from benzene/hexane gave colorless crystals of (**2**), m.p 177-179°C. MS/EI ($M^{\cdot+}$) *m/z* 366 (6%), 211 (58), 179 (100), 178 (82), 165 (24), 122 (23); ^{1}H NMR (300 MHz), see Table 1, IR (KBr) 1460, 1235, 1190, 1170, 1145, 1060, 1000, 950, 910, 895, 875, 840, 800, 760, 754, 740, 720, 695 Calcd for $C_{22}H_{19}FS_2$: C, 68 26, H, 5.73% Found· C, 68.61; H, 5.63%.

2,17-Dithia[3.3]biphenyleno(2,2')(1,4)cyclophane (3) The product (**3**) (0.35 g, 51%) was prepared from (**7**) and (**10**) as described in the general procedure. Recrystallization from benzene/hexane gave colorless crystals of (**3**), m.p 85-87°C MS/EI ($M^{\cdot+}$) *m/z* 348 (7%), 244 (12), 212 (27), 211 (100), 198 (17), 197 (27), 179 (99), 178 (58), 166 (20), 165 (36), 136 (25), 135 (11), 104 (76), ^{1}H NMR (300 MHz), see Table 1, IR (KBr) 1480, 1435, 1235, 1196, 1160, 1096, 1010, 955, 780, 750, 704, 674 cm $^{-1}$. Calcd for $C_{22}H_{20}S_2$ C, 75.82, H, 5 78 Found C, 76 02; H, 5 81%

2,17-Dithia[3.3]biphenyleno(2,2')(1,2)cyclophane (4) The product (**4**) (0 43 g, 62%) was prepared from (**7**) and (**11**) as described in the general procedure. Recrystallization from benzene/hexane gave colorless crystals of (**4**), m.p 87-90°C MS/EI ($M^{\cdot+}$) *m/z* 348 (32%), 212 (15), 211 (16), 197 (10), 180 (21), 179 (46), 178 (31), 165 (30), 135 (100), 104 (22), ^{1}H NMR (300 MHz), see Table 1, IR (KBr) 1480, 1445, 1435, 1235, 1196, 1160, 1096, 780, 750, 705, 676 cm $^{-1}$ Calcd for $C_{22}H_{20}S_2$ C, 75 82; H, 5.78% Found. C, 75 48, H, 5 61%.

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