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Preparation of 3*e*,4,5,6*e*,7,8-Hexahydro[2.2]paracyclophane

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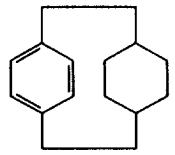
ABSTRACT: 3*e*,4,5,6*e*,7,8-Hexahydro[2.2]paracyclophane (**11**) was prepared through a coupling reaction to form dithiacyclophane, oxidation to yield the sulfone followed by the pyrolysis. It is noteworthy that the methine hydrogen in the rigid structures **5** and **11** toward to the center of the benzene ring leading to high field shifts resonance appear at δ -0.72 and -2.32 ~ -2.41. © 1997 Elsevier Science Ltd.

During the past three decades, the cyclophanes have been studied extensively. Recent reviews have collected the preparations, the properties, and the applications of various cyclophanes. The majority of pure hydrocarbon cyclophanes which have been reported contains two arene rings.[1] It is interesting for the comparison to obtain the compounds which contain a cyclohexane ring. In a previous work, we have prepared a paracyclophane bearing a benzene ring and a *cis*-cyclohexane ring bridged with two carbons, i.e. 3*a*,4,5,6*e*,7,8-hexahydro[2.2]paracyclophane (**1**).[2] Reduction of compound **1** tends to form monoene (**2**) presumably to release the strain energies from compound **1** or a possible intermediate diene. In this work, we synthesize its isomer, 3*e*,4,5,6*e*,7,8-hexahydro[2.2]paracyclophane (**11**) for the spectroscopic comparison.



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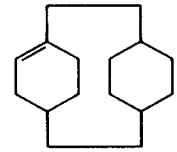

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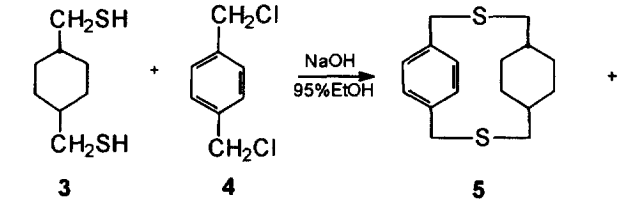
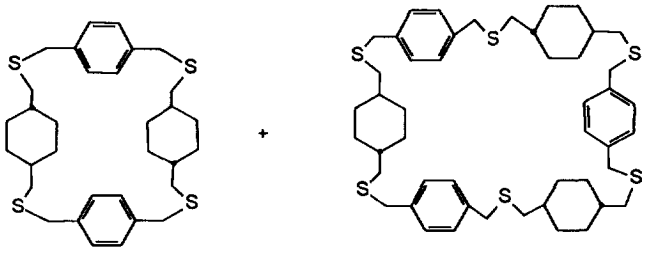
trans-1,4-Bis(mercaptomethyl)cyclohexane (**3**) was prepared from the reaction of the ditosylate of *trans*-1,4-bis(hydroxymethyl)cyclohexane with NaSH and H_2SO_4 in DMF.[3] The coupling reaction of α,α'-dichloro-*p*-

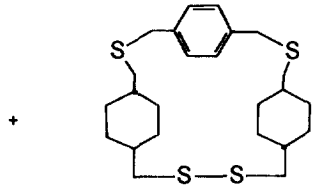
xylene (**4**) and compound **3** was carried out in an alcoholic NaOH solution, using the high dilution technique described by Davis.[4] The resultant solution was concentrated and separated chromatographically to give four white solid compounds: 2,11-dithia-4*e*,5,6,7*e*,8,9-hexahydro[3.3]paracyclophane (**5**), 2,11,20,29-tetrathia-4*e*,5,6,7*e*,8,9,22*e*,23,24,25*e*,26,27-dodecahydro[3.3.3.3]paracyclophane (**6**), 2,11,20,29,38,47-hexathia-4*e*,5,6,7*e*,8,9,22*e*,23,24,25*e*,26,27,40*e*,41,42,43*e*,44,45-octadecahydro[3.3.3.3.3.3]paracyclophane (**7**)[5] ,



3 **4** **5**



6 **7**



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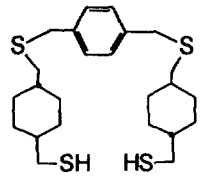
and 2,11,12,21-tetrathia-4*e*,5,6,7*e*,14*e*,15,16,17*e*,18,19-dodecahydro[3.4.3]paracyclophane (**8**)[6]. The coupling of α,α'-dichloro-*p*-xylene and *cis*-1,4-bis(mercaptomethyl)cyclohexane yielded only one compound.[7] This difference of product distribution from that of its *cis*-counterpart is due to the high strain energy resulting from the *trans*-conformation of the cyclohexane ring. The ^{1}H NMR displayed a higher field resonance at δ -0.72, and 0.53-0.61 for compounds **5** and **6**, respectively. This high field shift suggests that the *trans*-conformation of cyclohexane forces a proton to face to the benzene. Tetrathia compound **8** was confirmed by the reduction by using zinc/HOAc as a reducing reagent[8] to afford solid dithiol **10** in quantitative yield.



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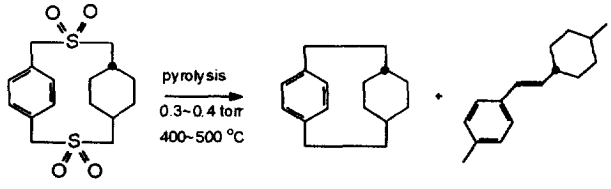
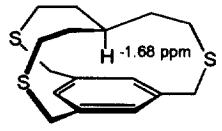
A number of methods can be applied for the extrusion of SO_2 along with the formation of either C-C or C=C bonds. The Ramberg-Backlund reaction[9] and its modification methods[10] yield the products with formation of double bonds from extrusion of SO_2 from 2,11-dithia-4*a*,5,6,7*e*,8,9-hexahydro[3.3]paracyclophane-2,2,11,11-tetraoxide.[2] This resultant compound was converted to a hyperstable monoene[11] under the catalytic hydrogen transfer reaction in a mixture of formic acid and triethylamine with 10% Pd/C as a catalyst. The combination of Stevens rearrangement and Hofmann elimination to transform sulfide linkages to carbon-carbon double bonds followed by catalytic hydrogenation is an alternative route.[12] The high strain characteristic of this series may resulting in a further hydrogenation as previously noted.[2] Pyrolysis is a direct process for the formation of C-C bond from sulfone series.[13] This process was employed for this work to prepare compound **11**.[14] In this work, compound **9** were first pyrolyzed at 400 ℃ for 20 min, and then at 500 ℃ for 30 min at 0.3-0.4 torr. During the process, products were collected in a cold-trap at -196 ℃. After chromatographical separation, 3*e*,4,5,6*e*,7,8-hexahydro[2.2]paracyclophane (**11**) was obtained as a minor (5%) and a ring-opened compound, *E*-1-(*trans*-4-methylcyclohexyl)-2-(4-tolyl)ethylene (**12**) was obtained as a major product (29%). The lower yields in the sulfur dioxide extrusion is not only due to the flexibility of the cyclohexane moiety but, more importantly, due to the lability of the nonbenzylic radical intermediates.



9 **11** **12**

The most interesting result is in the ^{1}H NMR spectroscopic analysis of compounds **5** and **11** , which displays a high field resonance with the signal at δ -0.72 and -2.36. The high-field shift of this proton suggests that it is more shielded by the benzene because of the shorter distance between that proton and the benzene ring after removing two sulfur atoms from dithiaparacyclophane **5**.[15] The proton resonance of the inner-methine in **11** (δ -2.36) is upfielded by 4.46 ppm from the methine resonance in the acyclic model compound

tris[(methylthio)methyl]methane (δ 2.06), or upfielded by 4.01 ppm from the methine resonance (1.65 ppm) in cyclophane **1** from the *cis*-cyclohexane counterpart. The ^{1}H NMR chemical shifts of compounds **5** and **11** are comparable to the hight ring-strained cyclophanes **13-17**.[16] From Johnson and Bovey's diagram, which estimates the magnitude of ring current effects on protons in various positions with respect to benzene rings, the distance from the inner-hydrogen to the center of the benzene ring was predicted to be ca. 2.45 A.[17]



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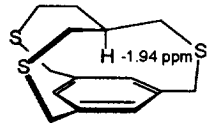

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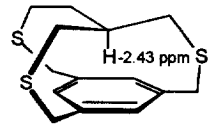

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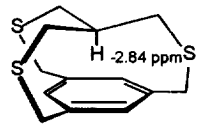

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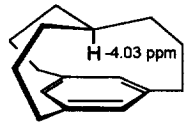

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The hydrogen is actually closer to the ring than it because the inner-methine hydrogen is not on the center as shown in Fig. 1. This structure was obtained from simulating by means of PM3 calculation method. The calculated distance from the center is 2.20 A.

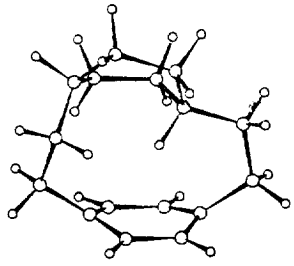

Figure 1. Simulated structure of compound **11** obtained from PM3 calculation.

Conclusion

Hexahydroparacyclophane can be prepared through a coupling of α,α'-dichloro-*p*-xylene and *trans*-1,4-bis(mercaptomethyl)cyclohexane followed by oxidization and pyrolysis. The fact that hexahydro[2.2]-paracyclohexane was obtained in low yield is due to the high ring strain of cyclohexane ring and the lability of

the nonbenzylic radical intermediates. The high field-shifted resonance of the methine hydrogen is resulted from the *trans*-conformation of cyclohexane. The higher ring strain of the *trans*-conformation leads to high yields of the larger ring coupling products.

Experimental

General. ^{1}H NMR spectra were recorded at 250 MHz, and ^{13}C NMR at 62.86 MHz at ambient temperature. Chemical shifts for the samples in deuteriochloroform solution are reported in δ units relative to tetramethylsilane. EI mass spectra were obtained on a JEOL JMS DX-300 double-focusing mass spectrometer at the ionization potentials of 70 eV. Samples were introduced via a direct insertion probe. FAB-MS spectra were obtained on the same spectrometer with *m*-nitrobenzyl alcohol as a solvent.

trans-1,4-Bis(mercaptomethyl)cyclohexane **3** was prepared from the reaction of *trans*-1,4-bis(tosylmethyl)cyclohexane and $NaSH.3H_2O$ in DMF solution in 63% yield. bp 122/5.8 torr.[3]

2,11-Dithia-4*e*,5,6,7*e*,8,9-hexahydro[3.3]paracyclophane **5** - A solution of compound **3** (1.24 g, 0.7 mmol) and α,α'-dichloro-*p*-xylene (1.87 g, 0.7 mmol) was added over a period of 70 h to a solution of NaOH (0.6 g, 1.5 mmol) in 95% ethanol (200 mL), using a high dilution technique. The solution was refluxed for an additional 2 h and then vacuum evaporated to give a viscous residue. The residue was extracted with CCl_4 (3 x 20 mL), dried over $MgSO_4$, filtered, and vacuum evaporated to give a waxy residue. The residue was separated chromatographically on silica gel with CH_2Cl_2/n-hexane (2/3 : V/V) as an eluent to yield 2,11-dithia-4*e*,5,6,7*e*,8,9-hexahydro[3.3]paracyclophane **5**, 2,11,20,29-tetrathia-4*e*,5,6,7*e*,8,9,22*e*,23,24,25*e*,26,27-dodecahydro[3.3.3.3]paracyclophane **6**, 2,11,20,29,38,47-hexathia-4*e*,5,6,7*e*,8,9,22*e*,23,24, 25*e*,26,27,40*e*, 41, 42,43*e*,44,45-octadecahydro[3.3.3.3.3.3]paracyclophane **7**, and 2,11,12,21-tetrathia-4*e*,5,6,7*e*,8,9,14*e*,15, 16,17*e*,18,19-dodecahydro[3.4.3]paracyclophane **8**.

Compound **5**, white solid, mp 114 ~ 115℃, yield 0.267g (13.5%); ^{1}H NMR δ -0.72(m, 1H), 0.57(m, 2H), 1.36 (m, 7H), 2.18(d, J=7.5 Hz, 2H), 2.21(d, J=8.8 Hz, 2H), 3.70(s, 2H), 3.72(s, 2H), 7.19(d, 2H, J=7.8 Hz), 7.28(d.2H,J= 7.8Hz); ^{13}C NMR 23.8, 24.9, 28.9, 30.0, 34.6, 36.3, 38.6, 39.8, 128.9, 130.8, 136.4, 140.1; EI MS(relative intensity) m/z 278(M^+,44), 141(9), 104(100); Anal. Calcd. for $C_{16}H_{22}S_2$: C, 69.01; H, 7.97. Found: C, 69.11; H, 7.94.

Compound **6**, white solid, mp 185~186℃; yield 1.10 g (58%); ^{1}H NMR δ 0.53~0.61 (m, 8H), 0.96(m, 7H), 1.57~1.60(m, 5H), 2.17(d, J=8.8 Hz, 8H), 3.60(s, 8H), 7.19(s, 8H); ^{13}C NMR δ 32.2, 36.7, 37.8, 38.5,128.8, 137.9; EI MS(relative intensity) m/z 556(M^+,44), 414(49), 141(60), 104(100); Anal. Calcd. for $C_{32}H_{44}S_4$: C,

69.01; H, 7.97. Found: C, 68.98; H, 7.99.

Compound **7**, white solid; mp 122~123℃; yield 0.23g (12%); ^{1}H NMR δ 0.80~0.93(m, 12H), 1.25~1.28(m, 10H), 1.79(d, 8H, J=6.8 Hz), 2.26(d, 12H, J=6.8 Hz), 3.65(s, 12H), 7.22(s, 12H); ^{13}C NMR δ 32.3,36.4, 37.5, 38.4,128.8, 137.2; FAB MS m/z (relative intensity) 835([M+1]$^+$,1), 429(88), 391(100); Anal. Calcd. for $C_{48}H_{66}S_6$: C, 69.01; H, 7.97. Found: C, 69.29; H, 7.44.

Compound **8**, white solid, mp 106.7~162.0℃, yield 0.134g (7%); ^{1}H NMR δ 0.68 (q, 4H, J=11.0 Hz), 0.81(q, 4H, J=11.0 Hz), 1.30~1.39(m, 4H), 1.85(d, 8H, J=11.0 Hz), 2.04(d, 4H, J=7.1 Hz), 2.40(d, 4H, J=7.1 Hz), 3.65(s, 4H), 7.21(s, 4H); ^{13}C NMR δ 31.7, 32.9, 36.6, 36.5, 36.9, 37.1, 37.9, 47.0, 129.0, 137.3; EI MS m/z (relative intensity) 452($M^{+\cdot}$,83), 141(37), 104(100); Anal. Calcd. for $C_{24}H_{36}S_4$: C, 63.66; H, 8.01. Found: C, 63.58; H, 8.32.

Reduction of compound **8** by using Zn/HOAc- A mixture of compound **8** (55.0 mg, 0.13 mmol) and zinc powder (16.8 mg, 0.26 mmol, activated) in glacial acetic acid (1.0 mL) was refluxed for 2 h. After being cooled to room temperature followed by the addition of water (30 mL), the mixture was extracted with $CHCl_3$ (30 mL x 3). The combined organic layer was washed with saturated Na_2CO_3, dried over $MgSO_4$, and the organic phase was evaporated to give the white solid of compound **10** (52 .0 mg, 94% yield), mp 52.0-53.3℃; ^{1}H NMR δ **0.90** (m, 8H), 1.29 (t, 2H, J = 7.6 Hz, S<u>H</u>), 1.28-1.33 (m, 4H), 1.87 (m, 8H), 2.30(4H, d, J = 6.7 Hz), 2.41 (dd, 4H, J=6.7, 7.6 Hz, C<u>H</u>$_2$SH), 3.65 (s, 4H), 7.23(s, 4H); ^{13}C NMR δ 31.3, 31.6, 32.3, 36.6, 37.6, 38.7, 40.9, 128.9, 139.2; IR 2639 cm^{-1}(ν_{SH}); EI MS m/z (relative intensity) 454(M^+, 14), 104(100); Anal. Calcd. for $C_{24}H_{38}S_4$: C, 63.38; H, 8.42. Found: C, 63.54; H, 8.33.

2,11-Dithia-4*e*,5,6,7*e*,8,9-hexahydro[3.3]paracyclophane-2,2-11,11-tetraoxide **9**. A mixture of **5** (1.0 g, 3.48 mmol), MCPBA (70% purity, 3.52 g, 14.3 mmol) and 20 mL of $CHCl_3$ was refluxed for 16 h. The solvent was removed by evaporation. The remaining solid was stirred with saturated. $Na_2S_2O_3$ (50 mL) for 10 min to quench the excess of MCPBA. The solid was collected by filtration and washed with water (30 mL x 3) and ether (30 mL x 3) to give 1.20 g (98.0% yield) of compound **9** as the white powder; mp 250℃(dec.); EI MS m/z (relative intensity) 342($M^{+\cdot}$,100); HRMS Calcd for $C_{16}H_{22}S_2O_4$ 342.0960, found 342.0959.

Pyrolysis of compound **9**: Compound **9** (0.5 g, 1.5 mmol) was placed in a quartz tube (2.5 cm o.d. x 120 cm length) with a cold trap for pyrolysis. The pyrolysis system was pre-evacuated to a pressure of 0.3-0.4 torr for 20 min and then the cold trap was cooled by means of liquid nitrogen. During pyrolysis, the temperature

was held at 400℃ for 20 min, and then at 500℃ for 30 min. After the trap was warmed to room temperature, the residue was dissolved in CH_2Cl_2 (30 mL x 3). A waxy material obtained from the CH_2Cl_2 solution was subjected for chromatographic separation on 20% $AgNO_3$ on Al_2O_3 (1.5 cm o.d. x 30 cm length) with hexane as an eluent to give 3*e*,4,5,6*e*,7,8-hexahydro[2.2]paracyclophane **11** and *E*-1-(*trans*-methylcyclohexyl)-2-(4-tolyl)ethylene **12.**

Compound **11**, white solid, mp 152-153℃, 16 mg (5 % yield); ^{1}H NMR δ -2.41 ~ -2.32 (m, 1H), 0.59 ~ 0.62 (m, 2H), 0.85 ~0.92 (m, 4H), 1.05 ~ 1.13(m, 4H), 1.20 ~1.49(m, 8H) 1.70 ~1.73(1H, m), 7.09(d, 2H, J=7.5Hz), 7.24(d, 2H, J=7.5Hz), ^{13}C NMR δ 22.6, 24.4, 28.6, 29.7, 31.7, 32.6, 37.1, 39.5, 130.5, 143.5, 143.9; EI MS m/z (relative intensity) 214(M^+,16), 104(100), 91(20); Anal. Calc. for $C_{16}H_{22}$: C, 89.65;H, 10.35. Found: C, 89.70; H, 10.42.

Compound **12**, viscous liquid; freezing point -38℃; 91 mg (29% yield); ^{1}H NMR δ 0.93 (d, 3H, J=6.8 Hz), 1.32~1.62 (m, 10H), 2.32 (s, 3H), 6.28 (dd, 1H, J=16.0, 5.7 Hz), 6.40 (d, 1H, J=16.0 Hz), 7.10 (d, 2H, J=7.8 Hz), 7.25 (d, 2H, J=7.8 Hz); ^{13}C NMR δ 20.3, 21.0, 29.2, 30.1, 30.8, 38.2, 125.8, 127.9, 129.1, 134.5, 135.3, 136.4; EI MS m/z (relative intensity) m/z 214(M^+,49), 118(51), 83 (100); Anal. Calcd. for $C_{16}H_{22}$: C,89.65; H, 10.35. Found: C, 89.51; H, 10.31.

Acknowledgment

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