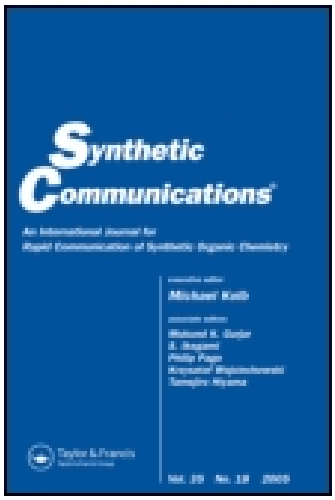

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NITROETHYLENOPHANES— NEW CLASS OF NOVEL CYCLOPHANES

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NITROETHYLENOPHANES— NEW CLASS OF NOVEL CYCLOPHANES

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ABSTRACT

Reaction of *o*-xylenyl dibromide with dipotassium salt of 2-nitro-1,1-ethanedithiol afforded nitroethylenophane **2**. Similar strategy has been used for the synthesis of cyclophanes **7**, **9** and **11**.

Synthesis of cyclophanes with heterocyclic building blocks resulting in Pyridinophanes,[1] Ureaphanes,[2] Benzimidazolophanes,[3] Piperazinophanes,[4] Benzotriazolophanes[5] has been recently reported. Such cyclophanes have promising properties[6] as molecular clefts and possesses favourable binding sites for metal ions and guest molecules. Recently, the field of molecular capsules has advanced to the stage where self-assembling through non-covalent interactions such as hydrogen bonds[7] and metal co-ordination[8]

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has proved to be a reliable tool. Though the synthesis of dipotassium salt of 2-nitro-1,1-ethanedithiol and its utility for the synthesis of ranitidine[9] and as histenine receptor[10] are known, its applicability for the synthesis of cyclophane with non- collapsible cavity is not known so far. Therefore, we wish to report herein the synthesis of new class of cyclophanes called nitroethylenophanes, which has a highly functionalized appendage that could be a potential tethering unit for non-covalent interaction.

Reaction of dipotassium salt of 2-nitro-1,1-ethanedithiol with *o*-xylenyl dibromide was carried out with a view to synthesize non-collapsible microcavity cyclophane **2**. The reaction mixture after stirring[11] in methanol and few drops of CH_2Cl_2 for 12 h and after usual workup gave cyclophane **2** in 40% yield. The benzylic protons are not equivalent and appeared as two singlets at δ 4.41 and 4.22 two protons each in ^{1}H NMR. Further, the olefinic proton appeared at δ 7.65 in addition to aromatic protons at δ 7.05 to 7.18. In ^{13}C NMR, also the two benzylic carbons are found to be non-equivalent and appeared at δ 37.5 and 39.2. One of the olefinic carbon appeared at δ 159.8 due to the deshielding effect of the nitro group. In mass spectrum, the molecular ion appeared at *m*/*z* 239. Though the spectral data can even account for the dimeric structure, the steel proof for the structure was arrived at from single crystal XRD.[12]

The cyclophane **2** was then reduced with $NaBH_4$ in ethanol with a view to modify the receptor–tethering unit. Treatment of nitroethylenophane **2** with $NaBH_4$ in EtOH gave nitroethanophane **3** as a colourless solid. In ^{1}H NMR, benzylic protons appeared as AB quartet at δ 4.40 and 3.81 and –C<u>H</u>C<u>H</u>$_2$NO$_2$ protons appeared as a multiplet at δ 4.61. The aromatic protons appeared as a multiplet at δ 7.12. Nitroethanophane **3** was then reduced with LAH to give the aminoethanophane **4** as a pale yellow liquid. The benzylic protons appeared along with the –C<u>H</u>– protons as a multiplet at δ 3.49 to 3.88 and the –C<u>H</u>$_2$NH$_2$ protons appeared as doublet at δ 3.04 in addition to the aromatic proton in ^{1}H NMR. The reaction sequence is shown in Scheme 1.

The above synthetic methodology has been applied for the synthesis of the cyclophane **7**. Nitroethylenophane **7** has been synthesized by two methods as shown in Scheme 2. Structure **7** has been confirmed on the basis of ^{1}H NMR.

Similar synthetic sequence when applied on *m*-terphenyl dibromide[13] resulted in the formation of nitroethylenophane **8** as a mixture of inseparable *syn* and *anti* isomers. The mixture was then reduced with $NaBH_4$ to yield the nitroethanophane **9** which is characterized by ^{1}H NMR. Similarly, the macrocyclic nitroethylenophane **10** was obtained as pale yellow solid in 30% yield from 2,6-*bis*(bromomethyl)-4-methylphenol[14] and dipotassium salt of 2-nitro-1,1-ethanedithiol (**1**). Cyclophane **10** was also found to be a

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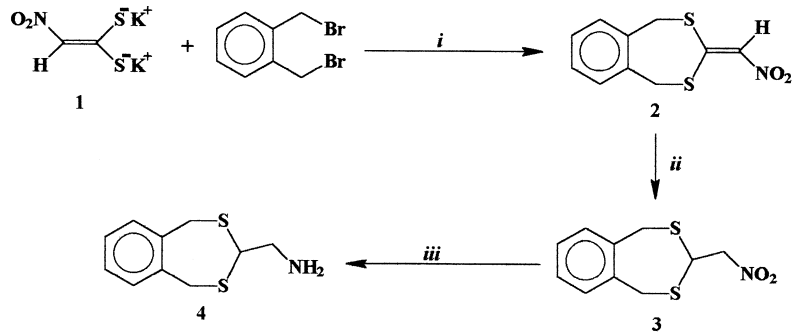
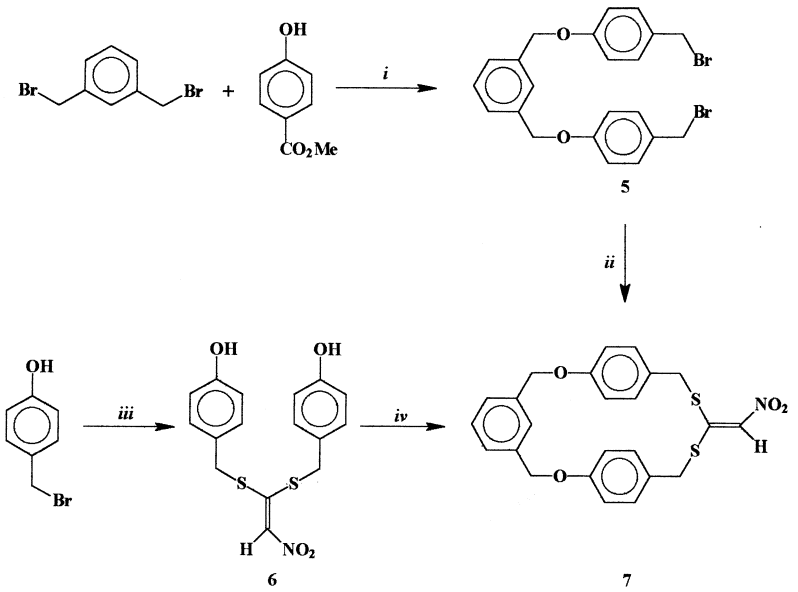


Scheme 1. Reagents and conditions: *i*. CH_3OH/CH_2Cl_2, r.t., 12 h, 40%; *ii*. $NaBH_4$, EtOH, r.t. 6 h, 85%; *iii*. $LiAlH_4$, THF, r.t. 6 h, 30%.



Scheme 2. Reagents and conditions: *i. a*) K_2CO_3/acetone, 48 h, 85%. *b*) $LiAlH_4$, THF, 6 h, 90%. *c*) PBr_3, CH_2Cl_3, r.t. 6 h, 95%; *ii*. $MeOH/CH_2Cl_2$, r.t, 24 h, 30%; *iii*. $MeOH/CH_2Cl_2$, r.t, 24 h, 63%; *iv*. *m*-xylenyl dibromide, K_2CO_3/acetone, r.t, 24 h, 25%.

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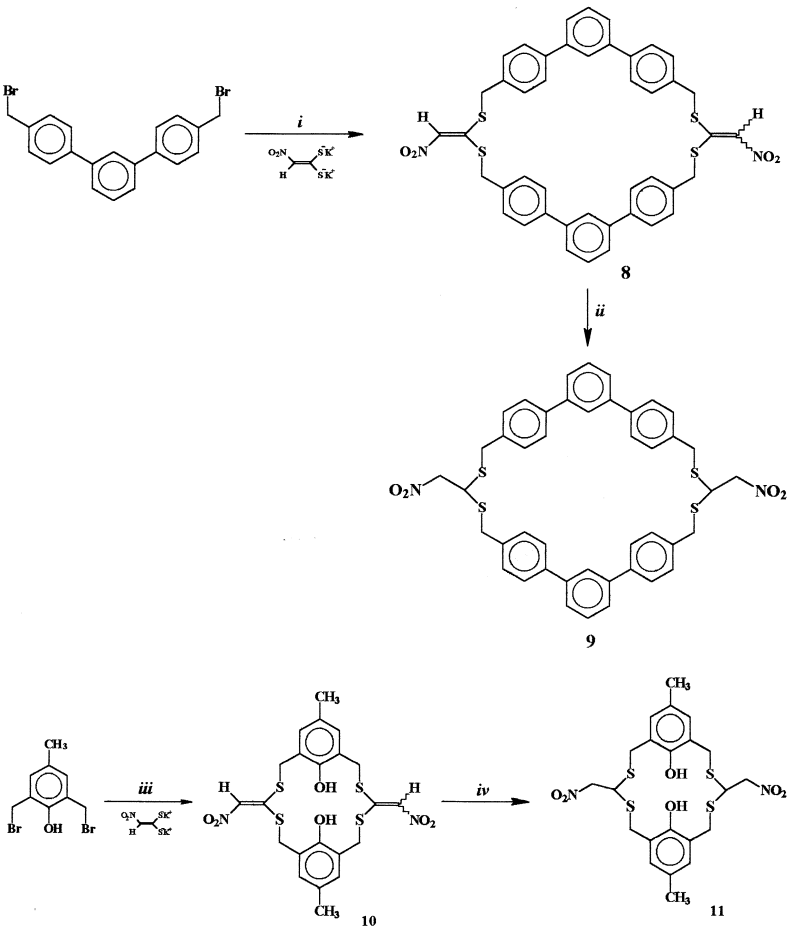
mixture of *syn* and *anti* isomers, which on reduction with $NaBH_4$ gave the nitroethanophane **11** as a colourless solid, characterized by spectral data. The reaction sequences are shown in Scheme 3.

Further studies on nitroethylenophanes as organic receptors are under investigation.



Scheme 3. Reagents and conditions: *i*. $MeOH/CH_2$, r.t. 24 h, 22%, *ii*. $NaBH_4$, EtOH, r.t, 12 h, 53%, *iii*. $MeOH/CH_2Cl_2$, r.t. 24 h, 30%; *iv*. $NaBH_4$, EtOH, r.t. 12 h, 45%.

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EXPERIMENTAL

General

All the melting points are uncorrected. The IR spectra were recorded using Shimadzu FT-IR 8300 instrument. The ^{1}H and ^{13}C NMR spectra of all compounds in $CDCl_3$ were recorded using Brucker (200 MHz) or Jeol (90 MHz) NMR spectrometer. The mass spectra were recorded using Hewlett–Packard 5985 (70 eV). The column chromatography was performed using silica gel (100–200 mesh).

Preparation of Dipotassium Salt of Nitroethenedithioacetate (1)

To a cooled and well stirred solution of carbon disulfide (20.8 mL, 0.37 mol) and nitromethane (17.6 mL, 0.32 mol), well dissolved potassium hydroxide (36.0 g) in 90 mL of dry methanol was added drop by drop over 40 min using a pressure equalizing funnel. The temperature was maintained at $-5^{\circ}C$ to $0^{\circ}C$ using ice salt mixture. Then the stirring was continued for 3 h. The brown colour solid formed was filtered though Buckner funnel as much as quickly to avoid the absorption of moisture. The residue was washed three times with dry methanol and three times with ether. The product was quickly transferred into a sample bottle, which was covered by a black paper to avoid the light decomposition of the sample. The yield of product obtained was 18.33 g, (27%). mp 210–211°C.

General Procedure for Preparation of Cyclophanes

To a well stirred solution of dipotassium salt of 2-nitro-1,1-ethanedithiol (**1**) (0.212 g, 1 mmol) in 20 mL of 50% aq. MeOH, corresponding dibromide (1 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. Then, the reaction mixture was concentrated to a minimum volume and water was added to form residue from which was extracted using CH_2Cl_2 (4×50 mL). The organic layer was thoroughly washed with water (3×100 mL); brine and dried over anhyd. Na_2SO_4. The dichloromethane was filtered and evaporated at reduced pressure to give the crude product, which was purified by column chromatography over silica gel.

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Synthesis of Nitroethylenophane 2

Following the general procedure, the nitroethylenophane **2** was obtained from *o*-xylylene dibromide. Yield: m.p. 96–98°C, IR (KBr) 3095, 1531, 1458, 1309, 1265, 1105, 769, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.22 (s, 2H), 4.41 (s, 2H), 7.05–7.18 (m, 4H), 7.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.4, 39.1, 128.1, 128.3, 129.6, 130.4, 133.5, 159.8; *m*/*z* 239 (m^+); Anal. Calcd. for $C_{10}H_9NO_2S_2$: C. 50.19, H, 3.79; N, 5.85. Found: C, 50.21, H, 3.82; N, 5.89.

Reduction of Nitroethylenophane 2 to Nitroethanophane 3 Using $NaBH_4$

The nitroethylenophane **2** (0.276 g, 1.1 mmol) was stirred with $NaBH_4$ (0.022 g, 0.6 mmol) in ethanol at room temperature for 6 h. Then the solution was acidified and evaporated to dryness. The solid mass obtained was purified by column chromatography over silica gel using 40% $CHCl_3$ in hexane to afford the nitroethanophane **3** in 85% yield. mp 107°C; IR (KBr) 3006, 2922, 1591, 1546, 1427, 1371, 1259, 1184, 765, 688 cm^{-1}, ^1H NMR (200 MHz): δ 3.81 and 4.40 (dd, 4H), 4.61 (m, 3H), 7.12 (m, 4H); ^{13}C NMR (50 MHz): δ 34.55, 56.02, 108.75, 127.24, 128.24, 129.20; *m*/*z* 241 (M^+); Anal. Calcd. for $C_{10}H_{11}NO_2S_2$: C, 49.77; H, 4.59; N, 5.80. Found: C, 49.87; H, 4.64; N, 5.84.

Reduction of Nitroethanophane 3 to Aminoethanophane 4 Using LAH

The nitroethanophane **2** (0.135 g, 0.55 mmol) was refluxed with $LiAlH_4$ (0.021 g, 0.56 mmol) in dry THF for 6 h. The reaction mixture was then treated with hydrated Na_2SO_4. The inorganic mass was filtered off and washed several times with THF. The THF was evaporated to afford the aminoethanophane **4** in 30% yield as a pale yellow liquid. IR ($CHCl_3$) 3354, 2923, 1654, 1444, 1043, 754 cm^{-1}, ^1H NMR (200 MHz): δ 3.04 (d, 2H), 3.49 and 3.88 (m, 5H), 7.19 (m, 4H); ^{13}C NMR (50 MHz): δ 24.88, 48.92, 71.65, 127.21, 128.24, 128.88; Anal. Calcd. for $C_{10}H_{13}NS_2$: C, 56.83; H, 6.20; N, 6.63. Found: C, 56.90; H, 6.24; N, 6.67.

Synthesis of Dibromide 5

The *m*-xylylene dibromide (2.64 g, 10 mmol) was treated *p*-hydroxymethylbenzoate (3.34 g, 22 mmol) in DMF and K_2CO_3 at 60°C for 48 h.

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Then the reaction mixture was diluted using large volume of water; the precipitated solid was extracted with CH_2Cl_2 (3×200 mL); washed with water and dried over anhyd. Na_2SO_4. The organic layer was filtered and evaporated to dryness to afford diester as a white solid in 85% yield. The diester (2.03 g, 5 mmol) was then treated with $LiAlH_4$ (0.265 g. 7 mmol) in THF at reflux for 8 h. The reaction mixture was treated with 20.0 g of hydrated Na_2SO_4. The reaction mixture was then filtered and the inorganic solid was washed with THF several times. All the THF was collected and evaporated to dryness to yield diol in 90%. The diol (0.7 g, 2 mmol) in CH_2Cl_2 was treated with PBr_3 (0.2 mL, 2 mmol) at room temperature for 8 h to afford the dibromide **5** in 95% yield.

Synthesis of Nitroethylenophane 7 from Dibromide 5

The nitroethylenophane **7** was obtained by following the general procedure from the dibromide **5** in 30% yield. mp 128°C; IR (KBr) 2931, 1604, 1512, 1450, 1303, 1228, 1172, 1091, 1016, 823 cm^{-1}, ^1H NMR (200 MHz): δ 3.36 (s, 4H), 4.41 (s, 2H), 5.10 (s, 2H), 7.11 (AB_q 8 Hz, 8H), 7.40 (m, 4H), 7.52 (s, 1H); Anal. Calcd. for $C_{24}H_{21}NO_4S_2$: C, 63.84; H, 4.69; N, 3.10. Found: C, 63.91; H, 4.82; N, 3.19.

Alternative Procedure for the Synthesis of 7

The *p*-hydroxybenzylbromide (1.87 g, 10 mmol) was treated with the nitroethylene dithioacetate (2.12 g, 10 mmol) in MeOH (60 mL) at room temperature for 24 h. The reaction mixture was then evaporated to dryness. The solid obtained was then purified over silica gel using 1:1 $CHCl_3$: hexane to give the diol **6** in 30% yield. The diol **6** (0.349 g, 1 mmol) was then treated with the *m*-xylylene dibromide (0.264 g, 1 mmol) in dry acetone (100 mL) at room temperature for 24 h. The reaction mixture upon usual work up afforded the nitroethylenophane **7** in 25% yield.

Synthesis of Cyclophane 8

Following the general procedure, the nitroethylenophane **8** was obtained from *m*-terphenyl dibromide in 22% yield. m.p. 131°C; IR (KBr) 2931, 1608, 1517, 1307, 1099, 1085, 790, 706, 466 cm^{-1}, ^1H NMR (200 MHz): δ 4.26 (s, 4H), 4.33 (s, 4H), 7.23–7.77 (m, 24H), 7.95 (s, 2H); ^{13}C NMR (50 MHz); δ 30.58, 57.80, 73.99, 105.78, 125.67, 126.79, 127.88,

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129.25, 137.17, 165.88; Anal. calcd. for $C_{44}H_{34}N_2O_4S_4$: C, 67.49; H, 4.38; N, 3.58. Found: C, 67.51; H, 4.48; N, 3.69.

Reduction of Nitroethylenophane 8 Using Sodium Borohydride

The nitroethylenophane **8** (0.1 g, 0.16 mmol) was stirred with $NaBH_4$ (0.012 g, 0.317 mmol) in ethanol at room temperature for 6 h. Then the solution was acidified and evaporated to dryness. The solid mass obtained was purified by column chromatography over silica gel using 40% $CHCl_3$ in hexane to afford the nitroethanophane **9** in 30% yield. m.p. 142°C; IR (KBr) 2932, 1606, 1517, 1458, 1312, 1230, 1171, 1098, 1017, 823, 790 cm^{-1}; ^1H NMR (200 MHz): δ 4.11 (s, 4H), 4.21 (s, 4H), 4.42–4.54 (m, 6H), 7.10–7.62 (m, 24H); Anal. Calcd. for $C_{44}H_{38}N_2O_4S_4$: C, 67.15; H, 4.87; N, 3.56. Found: C, 67.21; H, 4.89; N, 3.61.

Synthesis of Cyclophane 10

Following the general procedure, the nitroethylenophane **10** was obtained from 2,6-(bromomethyl)4-methylphenol in 30% yield. m.p. 91°C; IR (KBr) 3396, 2942, 1526, 1458, 1309, 1265, 1162, 1105, 770, 708 cm^{-1}; ^1H NMR (200 MHz): δ 2.28 (s, 6H), 3.35 (s, 4H), 4.52, (s, 4H), 6.98 (s, 2H), 7.52 (s, 2H); ^{13}C NMR (50 MHz): δ 29.70, 58.28, 71.86, 117.88, 123.28, 128.69, 129.02, 165.50; Anal. Calcd. for $C_{22}H_{22}N_2O_6S_4$: C, 49.05; H, 4.12; N, 5.20. Found: C, 49.08; H, 4.15; N, 5.24.

Reduction of Nitroethylenophane 10 Using Sodium Borohydride

The nitroethylenophane **10** (0.107 g, 0.2 mmol) was stirred with $NaBH_4$ (0.015 g, 0.4 mmol) in ethanol at room temperature for 6 h. Then the solution was acidified and evaporated to dryness. The solid mass obtained was purified by column chromatography over silica gel using 40% $CHCl_3$ in hexane to afford the nitroethanophane **11** in 45% yield. m.p. 108°C; IR (KBr) 3386, 2934, 1606, 1517, 1456, 1312, 1222, 1171, 1091, 1017, 823, 790 cm^{-1}; ^1H NMR (200 MHz): δ 2.26 (s, 6H), 3.99 (s, 4H), 4.11, (s, 4H), 4.66–4.71 (m, 6H), 6.92 (s, 4H); Anal. Calcd. for $C_{22}H_{26}N_2O_6S_4$: C, 48.69; H, 4.83; N, 5.16. Found: C, 48.72; H, 4.84; N, 5.19.

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11. It is noteworthy to mention that the conventional procedure of slow addition for the synthesis of cyclophanes should be avoided. During slow addition, the predominant product is found to be $O_2NCH{=}C(SMe)\text{-}C(SMe){=}CHNO_2$ and the results of such investigation will be communicated later.
12. The other details regarding XRD analysis will appear as a separate communication as it is carried out as a collaborative work with the Department of Bio-Physics and Crystallography, University of Madras, Guindy Campus, Chennai – 600 025.
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