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Synthesis of intra-annularly functionalized cationic pyridinophanes

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Abstract—The precyclophane **1** derived from 2,6-bis(bromomethyl)pyridine and 2.1 equiv. of benzimidazole afforded pyridinobenzimidazolophanes **6–8** on further reaction with 1 equiv. of 2,6-bis(bromomethyl)pyridine, 3,5-bis(bromomethyl)anisole and 1,3-bis(bromomethyl)-4-nitrophenol, respectively. A similar synthetic strategy was used for the synthesis of pyridinobenzotriazolophanes **9–11**. Potential receptors **16** and **17** were also synthesized. © 2002 Elsevier Science Ltd. All rights reserved.

Cyclophanes with heterocyclic ring systems possess binding sites for metal ions[1] and hence can have promising features[2] as molecular hosts. Pyridinophanes have been synthesized by a variety of methods[3] and used as model systems to study the diastereo- and enantioselectivity of certain biochemically important reactions.[4] Use of benzimidazole,[5] benzotrioazole[6] for the synthesis of cyclophanes has also been recently reported. The use of pyridyl units in host compounds and their host–guest complexation properties have also been studied.[7] We report herein the synthesis of a new class of positively charged receptors containing pyridyl units with either imidazole or triazole building blocks.

Reaction of 2.1 equiv. of benzimidazole with 1 equiv. of 2,6-bis(bromomethyl)pyridine[8] in the presence of aq. NaOH gave the precyclophane **1** in 62% yield. ^{1}H NMR of **1** showed a singlet at δ 5.44 for $-NCH_2-$ protons, the pyridine protons appeared as a doublet at δ 6.87 integrating for two protons and a one proton triplet was observed at δ 7.51 in addition to the aromatic protons. Proton decoupled ^{13}C NMR of **1** showed the $-NCH_2-$ carbon at δ 50.3 in addition to seven aromatic carbons. Treatment of the precyclophane **1** with 1 equiv. of 2,6-bis(bromomethyl)pyridine in CH_3CN under reflux for five days afforded the pyridinophane **6** in 90% yield. ^{1}H NMR of pyridinophane **6** displayed a singlet at δ 5.85 for $-NCH_2-$ protons and the imidazole proton ($-N-CH{=}N-$) appeared as a singlet at δ 9.68 in addition to the aromatic protons. The NCH_2- appeared at δ 49.1 in ^{13}C NMR in addition to seven aromatic carbons. Precyclophane **1** was then refluxed with 3,5-bis(bromomethyl)anisole in CH_3CN for five days. The reaction mixture after usual workup afforded the pyridinophane **7** in 68% yield. Similarly, reaction of **1** with 1,3-bis(bromomethyl)-4-nitrophenol[9] gave the pyridinophane **8** in 58% yield. In order to test the other route, precyclophane **2** was prepared by stirring benzimidazole with 3,5-bis(bromomethyl) anisole in CH_3CN in the presence of NaOH. In ^{1}H NMR, the precyclophane **2** displayed a singlet for three protons at δ 3.63 for OCH_3 and the $-NCH_2-$ appeared as another singlet at δ 5.22 in addition to the aromatic protons. Off resonance decoupled ^{13}C NMR showed the $-NCH_2-$ at δ 48.5 and the OCH_3 at δ 55.3 along with other aromatic carbons. Macrocyclization of **2** with 2,6-bis(bromomethyl)pyridine in CH_3CN for five days afforded the pyridinophane **7** in 65% yield (Scheme 1).

In order to test the synthetic utility of the above sequence for the synthesis of pyridinobenzotriazolophanes, the precyclophane **3** was prepared from 2,6-bis(bromomethyl)pyridine and benzotriazole in 39% yield. Coupling of the precyclophane **3** with one more equivalent of 2,6-bis(bromomethyl)-pyridine, 3,5-bis(bromomethyl)anisole and 1,3-bis-(bromomethyl)-4-nitrophenol gave the pyridinophanes **9–11** in 42, 59 and 52% yields, respectively (Scheme 2).

Similarly, pyridinophanes **12–14** were also prepared from precyclophane **4** and 2,6-bis(bromomethyl)pyridine, 3,5-bis(bromomethyl)anisole and 1,3-bis(bromomethyl)-4-nitrophenol in 54, 57 and 45% yields, respectively. Precyclophane **4** was obtained in 37% yield by the reaction of 2,6-bis(bromomethyl)pyridine with 2.1 equiv. of imidazole.

The protonated version of cyclophane **12** was obtained by reaction with CF_3COOH in D_2O. The diprotonated cyclophane salt **15** was identified by ^{1}H NMR. The imidazole proton appeared as usual at δ 7.68 and 9.46, however, the

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Keywords: imidazole; benzotriazole.

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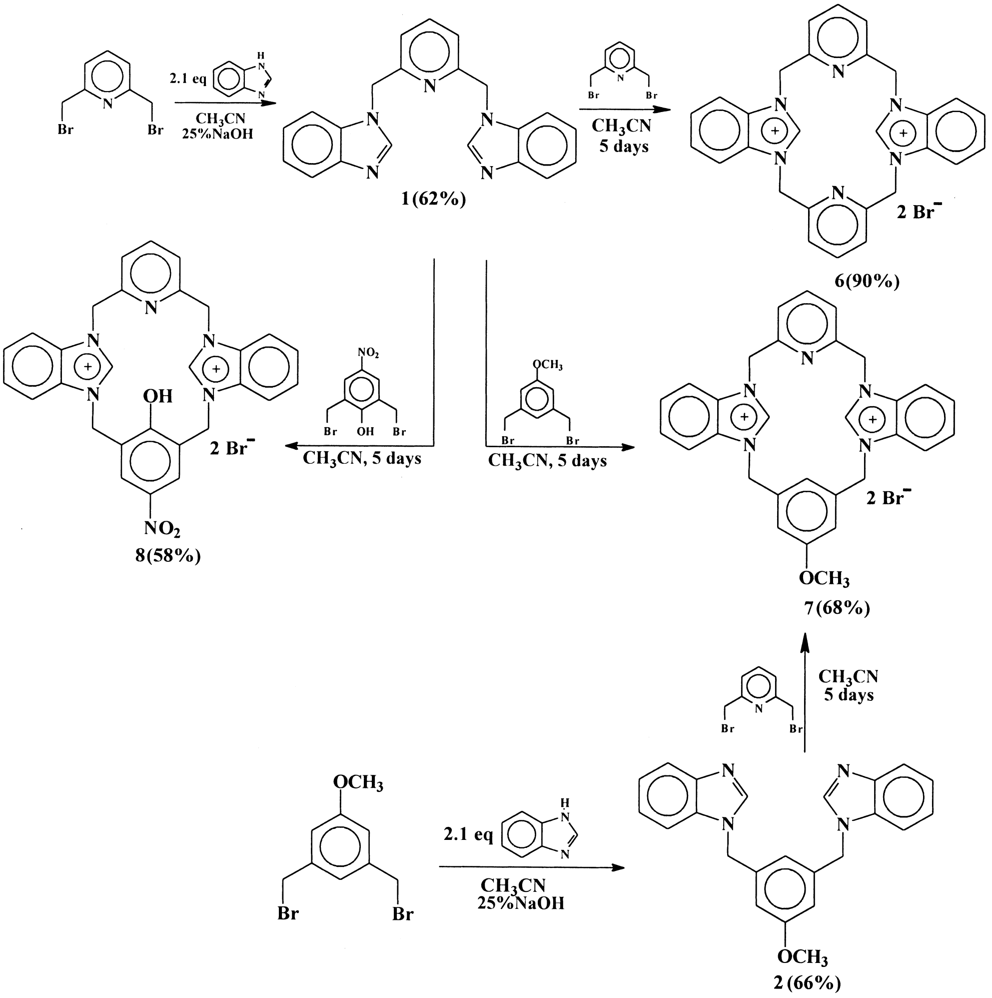


Scheme 1.

pyridine protons appeared at δ 8.21 as a doublet for 4H and δ 8.64 for 2H as a triplet, illustrating the deshielding effect caused by protonation[10] (Scheme 3).

Finally, receptors **16** and **17** with large cavities were synthesized from 2,6-bis(bromomethyl)pyridine in 33 and 69% yields, respectively, by the following sequence (Scheme 4).

It is worthy of note that pyridinoimidazolophanes **16** and **17** could be receptors for aliphatic amino acids and dicarboxylic acids. Synthesis of other macrocyclic pyridinophanes and investigation of their receptor activities are under investigation.

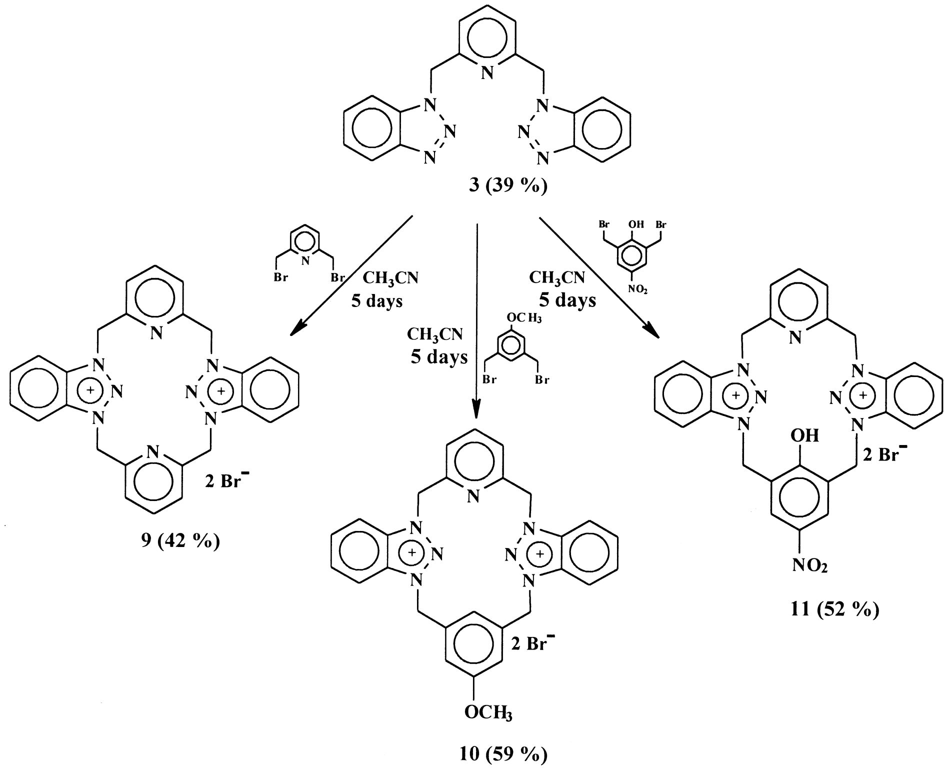
1. Experimental

All the melting points are uncorrected. ^{1}H and ^{13}C NMR were obtained on Jeol GSX 400 MHz or Bruker DPX 300 MHz instrument with $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are expressed in ppm using TMS as internal standard. Coupling constant (J) values are given in Hz. IR spectra were recorded on Shimadzu FT-IR-8300 instrument. The mass spectra were recorded using Jeol (EI, 70 eV), FAB mass spectra on JEOL SX 102/DA-6000 using *m*-nitrobenzyl alcohol (NBA) as matrix and MALDI mass spectra on KRATOS PCKompact SEQ V1.2.2 using α-cyanocinnamic acid (CCA). Acetonitrile was freshly dried prior to use. The precyclophanes were purified using neutral alumina column chromatography.

1.1. General procedure for the synthesis of precyclophanes

To the solution of imidazole/benzimidazole/benztriazole (20 mmol) in acetonitrile (50 mL), NaOH solution (10 mL, 25%) was added and stirred for 10 min. The dibromide (10 mmol) in acetonitrile (10 mL) was added at once and stirred for two days at room temperature. After the completion of the reaction, the reaction mixture was evaporated in vacuo, extracted with $CHCl_3$ (4×50 mL), washed with brine (2×50 mL) and dried ($MgSO_4$), the solvent was evaporated in vacuo. The crude product was purified by column chromatography on neutral alumina using $CH_3OH/CHCl_3$ (1:99) for precyclophanes **1**, **2**, **4**, **5** and EtOAc/hexane (1:4) for precylophane **3** as eluting solvent.

1.1.1. Precyclophane 1. 62%, Colourless solid, mp 106–108°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.44 (s, 4H, NCH_2), 6.87 (d, 2H, J=7.7 Hz), 7.51 (t, 1H, J=7.7 Hz), 7.80 (s, 2H), 8.00 (s, 2H); ^{13}C NMR δ_C (75.47 MHz, $CDCl_3$) 50.3, 109.9, 120.4, 120.5, 122.4, 123.3, 138.5, 155.7; m/z (EI, 70 eV)

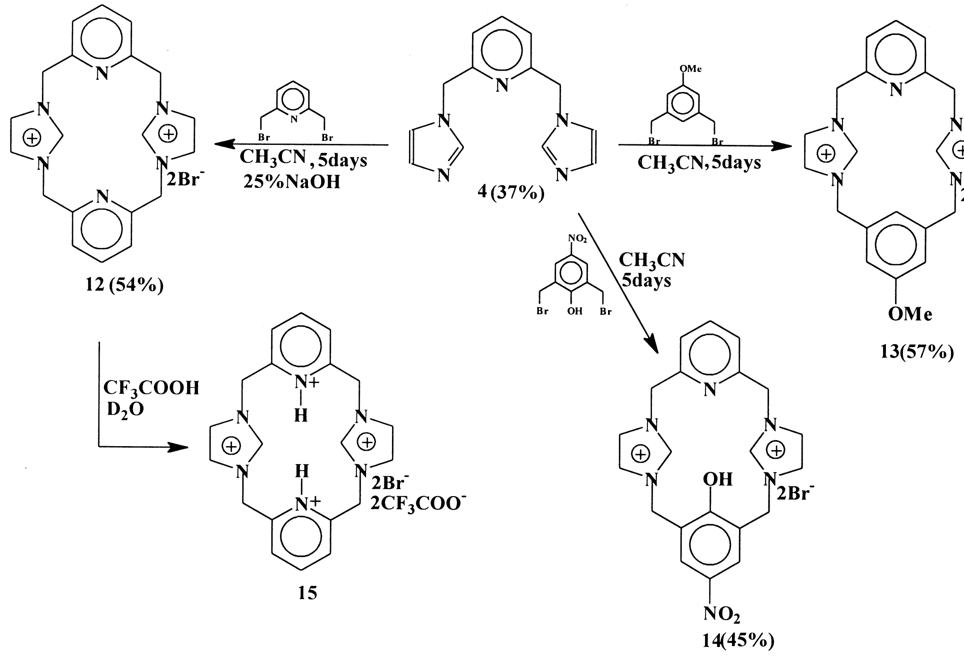


Scheme 2.

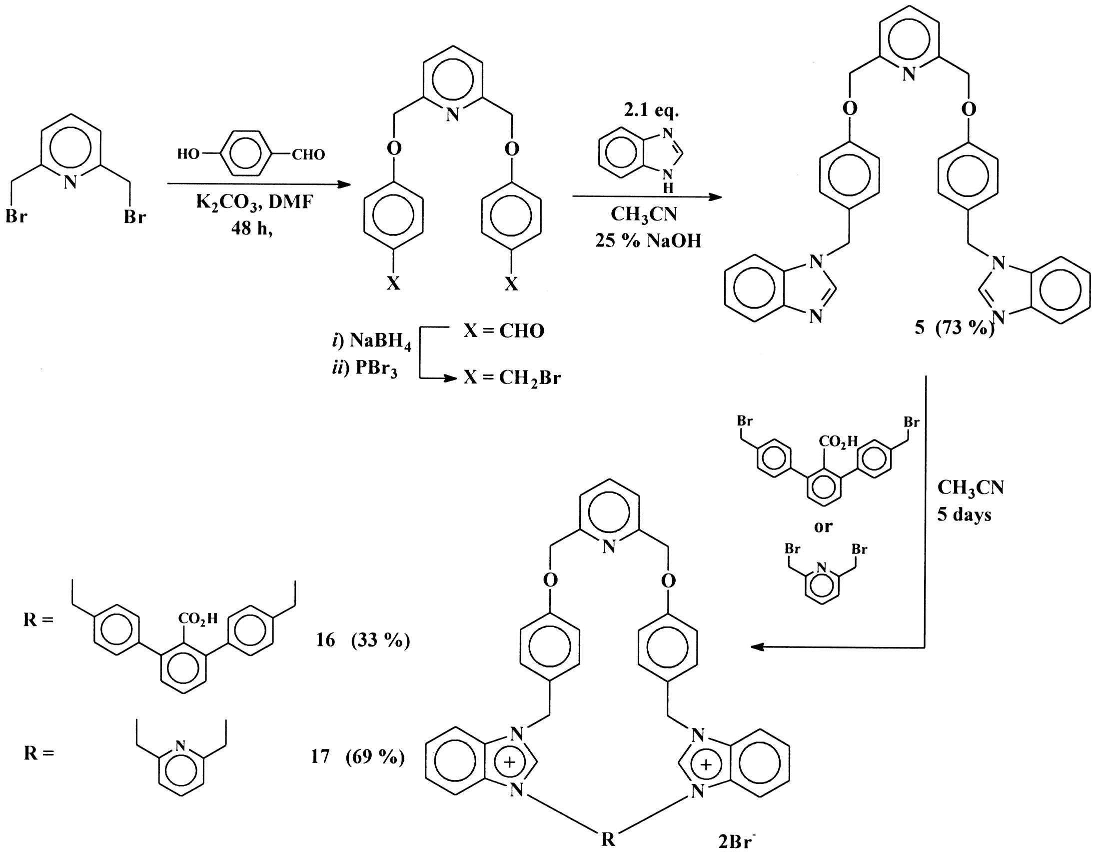
339 (M^+); Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63; Found: C, 74.20, H, 4.97, N, 20.33.

1.1.2. Precyclophane 2. 66%, Colourless solid, mp 179–181°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.63 (s, 3H, $-OCH_3$), 5.22 (s, 4H, NCH_2), 6.58 (d, 3H, J=6.8 Hz), 7.24 (m, 6H), 7.82 (d, 2H, J=7.5 Hz), 7.89 (s, 2H); ^{13}C NMR δ_C (75.47 MHz, $CDCl_3$) 48.5, 55.3, 109.9, 112.4, 117.8, 120.5, 122.4, 123.2, 138.0, 143.1, 143.9, 160.7; m/z (EI, 70 eV) 368 (M^+); Anal. Calcd for $C_{19}H_{15}N_7$: C, 66.85; H, 4.43; N, 28.72; Found: C, 66.61; H, 4.28, N, 28.58.

1.1.3. Precyclophane 3. 39%, Colourless solid, mp 119–121°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.92 (s, 4H, NCH_2), 7.05 (d, 2H, J=7.7 Hz), 7.36 (s, 6H), 7.57 (t, 1H, J=7.7 Hz), 8.05 (m, 2H); ^{13}C NMR δ_C (75.47 MHz, $CDCl_3$) 53.4, 109.7, 120.0, 121.4, 123.9, 127.4, 133.0, 138.4, 146.1, 154.8; m/z (EI, 70 eV) 341 (M^+); Anal. Calcd for



Scheme 3.



Scheme 4.

$C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21; Found: C, 75.10, H, 5.31, N, 14.98.

1.1.4. Precyclophane 4. 37%, Colourless solid, mp 59–61°C; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.21 (s, 4H, -*NCH*$_2$), 6.87 (d, 2H, J=7.7 Hz), 6.95 (s, 2H), 7.08 (s, 2H), 7.59 (m, 3H); ^{13}C NMR δ_C (75.47 MHz, $CDCl_3$) 52.1, 119.3, 120.2, 129.9, 137.5, 138.5, 156.3; *m/z* (EI, 70 eV) 239 (M^+); Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27; Found: C, 65.19; H, 5.32; N, 28.96.

1.1.5. Precyclophane 5. 73%, Colourless solid, mp 142–145°C; ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 5.17 (s, 4H -*O*CH$_2$), 5.27 (s, 4H, -*NCH*$_2$), 6.94 (d, 4H, J=8.8 Hz), 7.13 (d, 4H, J=8.8 Hz), 7.23–7.31 (m, 6H), 7.42 (d, 2H, J=7.8 Hz), 7.72 (t, 1H, J=7.8 Hz), 7.81 (d, 2H, J=6.7 Hz), 8.10 (d, 2H,); ^{13}C NMR δ_C (100.40 MHz, $CDCl_3$) 48.3, 70.5, 110.0, 115.2, 120.2, 120.3 122.2, 123.0 127.9, 128.6, 133.8, 137.7, 143.0, 143.8, 156.4, 158.2; *m/z* (EI, 70 eV) 551 (M^+); Anal. Calcd for $C_{35}H_{21}N_5O_2$: C, 76.20; H, 5.30; N, 12.70. Found: 76.20; H, 5.19, N, 12.55.

1.2. General procedure for the synthesis of cyclophanes

To the solution of precyclophanes (6 mmol) in dry acetonitrile (400 mL), dibromide (6 mmol) was added in one portion and refluxed for five days. After completion of the reaction, the cyclophane was obtained by filtration of the reaction mixture. The cyclophane was thoroughly washed with acetonitrile and dried in vacuo.

1.2.1. Cyclophane 6. 90%, Colourless solid, >300°C decomp.; ^{1}H NMR δ_H (300 MHz, DMSO-d_6) 5.84 (s, 8H), 7.33 (bs, 8H), 7.91 (bs, 4H), 8.11 (bs, 2H), 9.68 (s, 2H); ^{13}C NMR δ_C (75.47 MHz, DMSO-d_6) 49.1, 112.1, 121.7, 125.3, 129.4, 137.6, 142.0, 151.7; *m/z* (MALDI-MS, CCA) 444.9 (M^+-2Br); Anal. Calcd for $C_{28}H_{24}N_6Br_2$: C, 55.63; H, 3.97; N, 13.91. Found: C, 55.55; H, 3.77; N, 14.01.

1.2.2. Cyclophane 7. 68%, Colourless solid, 296–298°C decomp.; ^{1}H NMR δ_H (300 MHz, DMSO-d_6) 3.89 (s, 3H), 5.73 (s, 4H), 5.84 (s, 4H), 7.33–8.13 (m, 14H); ^{13}C NMR δ_C (75.47 MHz, DMSO-d_6) 49.5, 50.9, 56.0, 111.93, 113.9, 114.2, 115.19, 123.9, 127.1, 127.2, 130.8, 131.2, 137.1, 139.2, 143.1, 153.5, 160.2; *m/z* (FAB-MS, NBA) 553 (M^+-Br), 473 (M^+-2Br); Anal. Calcd for $C_{30}H_{27}N_5OBr_2$: C, 56.87; H, 4.27; N, 11.06. Found: C, 56.65; H, 4.09; N, 10.92.

1.2.3. Cyclophane 8. 58%, pale yellow solid, 260–262°C decomp.; IR ν_{max}(KBr); 3414; ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 5.72 (s, 8H), 7.29– 7.64 (m, 4H), 7.80 (d, 2H, J=8.3 Hz), 7.85 (d, 2H, J=7.8 Hz), 8.04 (t, 1H, J=7.8 Hz), 8.19 (d, 2H, J=8.3 Hz), 8.73 (s, 2H), 9.46 (s, 2H); ^{13}C NMR δ_C (100.40 MHz. DMSO-d_6) 47.0, 50.4, 113.7, 114.2, 122.9, 123.8, 126.8, 129.5, 130.8, 131.2, 139.0, 143.0, 153.3; *m/z* (FAB-MS, NBA) 584 (M^+-Br), 504 (M^+-2Br); Anal. Calcd for $C_{29}H_{24}N_6O_3Br_2$: C, 52.41; H, 3.62; N, 12.65. Found: C, 52.25; H, 3.55; N, 3.66.

1.2.4. Cyclophane 9. 42%, Colourless solid, 257–259°C decomp.; ^{1}H NMR δ_H (300 MHz, DMSO-d_6) 6.38 (s, 8H),7.62 (s, 4H), 7.65 (s, 4H), 7.76 (d, 4H, J=11.9 Hz), 8.07–8.13 (m, 2H).; ^{13}C NMR δ_C (75.47 MHz, DMSO-d_6) 54.7, 113.9, 122.9, 131.5, 134.9, 139.2, 152.6; m/z (FAB-MS, NBA) 526 (M$^+$−Br), 446 (M$^+$−2Br); Anal. Calcd for $C_{26}H_{22}N_8Br_2$: C, 51.49; H, 3.63; N, 18.48. Found: C, 51.11; H, 3.55; N, 18.51.

1.2.5. Cyclophane 10. 59%, Colourless solid, 249–251°C decomp.; ^{1}H NMR δ_H (300 MHz, DMSO-d_6) 3.87 (s, 3H), 6.24 (s, 4H), 6.35 (s, 4H), 7.41 (s, 2H), 7.75 (s, 4H), 7.92 (d, 2H, J=7.58 Hz), 8.03–8.13 (m, 6H); ^{13}C NMR δ_C (75.47 MHz, DMSO-d_6) 53.8, 54.92, 55.67, 113.7, 114.0, 114.9, 115.9, 124.1, 131.4, 131.53, 133.9, 134.7, 135.2, 139.2, 152.0, 160.0; m/z (MALDI-MS, CCA) 475.9 (M$^+$−2Br); Anal. Calcd for $C_{28}H_{25}N_7OBr_2$: C, 52.91; H, 3.94; N, 15.43; Found: C, 52.66; H, 3.81; N, 15.62.

1.2.6. Cyclophane 11. 52%, pale yellow solid, 202–204°C decomp.; IR ν_{max}(KBr); 3417; ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 6.25 (s, 4H), 6.32 (s, 4H), 7.92–8.41 (m 11H) 8.86 (s, 2H) ^{13}C NMR δ_C (100.40 MHz, DMSO-d_6) 51.9, 52.7, 113.8, 114.0, 114.9, 121.7, 124.6, 129.6, 130.2, 131.2, 131.5, 134.3, 134.5, 152.1, 152.2; m/z (FAB-MS, NBA) 586 (M$^+$−Br), 506 (M$^+$−2Br); Anal. Calcd for $C_{27}H_{22}N_8O_3Br_2$: C, 48.65; H, 3.30; N, 16.82; Found: C, 48.55; H, 3.25; N, 16.99.

1.2.7. Cyclophane 12. 54%, Colourless solid, 300–302°C decomp.; ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 5.63 (s, 8H), 7.59 (d, 4H, J=7.8 Hz), 7.64 (d, 4H, J=1.5 Hz), 7.97 (t, 2H, J=7.8 Hz), 9.21 (s, 2H); ^{13}C NMR δ_C (100.40 MHz. DMSO-d_6) 52.3, 122.5, 123.3, 137.0, 138.5, 153.3; m/z (FAB-MS, NBA) 424 (M$^+$−Br), 344 (M$^+$−2Br); Anal. Calcd for $C_{20}H_{20}N_6Br_2$: C, 47.62; H, 3.97; N, 16.67; Found: C, 47.51; H, 3.85; N, 16.88.

1.2.8. Cyclophane 13. 57%, Colourless solid, 284–286°C decomp.; ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 3.86 (s, 3H), 5.50 (s, 4H), 5.62 (s, 4H), 6.13 (s, 1H), 7.20 (s, 2H), 7.71 (d, 2H, J=7.8 Hz), 7.79 (s, 2H), 7.83 (s, 2H), 8.07 (t, 3H, J=7.8 Hz), 9.32 (s, 2H); ^{13}C NMR δ_C (100.40 MHz. DMSO-d_6) 51.4, 52.7, 55.6, 113.6, 115.5, 123.0, 123.5, 136.7, 137.9, 138.7, 153.6, 159.6; m/z (FAB-MS, NBA) 453 (M$^+$−Br), 373 (M$^+$−2Br); Anal. Calcd for $C_{22}H_{23}N_5OBr_2$: C, 49.53; H, 4.32; N, 13.33; Found: C, 49.13; H, 4.11; N, 13.55.

1.2.9. Cyclophane 14. 45%, pale yellow solid, 228–230°C decomp.; IR ν_{max}(KBr); 3433; ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 5.49 (s, 4H), 5.62 (s, 4H), 7.64 (d, 2H, J=7.8 Hz), 7.70 (s, 2H), 7.79 (s, 2H), 7.96 (t, 1H, J=7.8 Hz), 8.36 (s, 2H), 8.87 (s, 2H); ^{13}C NMR δ_C (100.40 MHz. DMSO-d_6) 48.8, 52.6, 113.7, 122.5, 123.2 123.5, 123.8, 129.0, 136.3, 138.8, 153.8, 217.7; m/z (FAB-MS, NBA) 476 (M$^+$−Br), 396 (M$^+$−2Br); Anal. Calcd for $C_{21}H_{20}N_6O_3Br_2$: C, 44.68; H, 3.55; N, 14.89; Found: C, 44.45; H, 3.33; N, 14.99.

1.2.10. Cyclophane 15. ^{1}H NMR δ_H (200 MHz, D_2O) 6.07 (s, 8H), 7.68 (s, 4H), 8.21 (d, 4H, J=7.8 Hz), 8.64 (t, 2H, J=7.8 Hz), 9.46 (s, 2H); ^{13}C NMR δ_C 52.4, 122.4, 123.4, 138.6, 151.9, 159.6; Anal. Calcd for $C_{24}H_{22}Br_2F_6N_6O_4$: C, 39.36; H, 3.03; N, 11.48; Found: C, 38.99, H, 2.97, N, 11.23.

1.2.11. Cyclophane 16. 33%, Colourless solid, 223–225°C decomp.; IR ν_{max}(KBr); 1712, 3415; ^{1}H NMR δ_H (400 MHz, DMSO-d_6) 5.1 (s, 4H), 5.77 (s, 4H), 5.88 (s, 4H), 7.02–8.33 (m, 30H), 10.30 (s, 2H); ^{13}C NMR δ_C (100.40 MHz. DMSO-d_6) 49.3, 49.5, 70.3, 114.0, 114.2, 115.2, 121.2, 126.4, 127.0, 127.6, 129.0, 129.2, 130.1, 130.9, 131.1, 133.7, 138.0, 140.3, 142.5, 156.0, 158.4, 169.8; m/z (MALDI-MS, CCA) 852.7 (M$^+$−2Br); Anal. Calcd for $C_{56}H_{45}N_5O_4Br_2$: C, 66.47; H, 4.45; N, 6.92; Found: C, 66.09; H, 4.35; N, 7.09.

1.2.12. Cyclophane 17. 69%, Colourless solid, 208–210°C decomp.; ^{1}H NMR δ_H (200 MHz, DMSO-d_6) 5.03 (s, 4H), 5.71 (s, 4H), 5.81 (s, 4H), 7.38–7.89 (m, 22H), 10.20 (s, 2H); ^{13}C NMR δ_C (50.33 MHz. DMSO-d_6) 48.24, 49.53, 68.46, 111.98, 112.29, 114.26, 119.50, 121.31, 123.98, 125.14, 128.33, 129.22, 129.68, 141.14, 151.19, 154.19, 156.82; m/z (FAB, NBA) 736 (M$^+$−Br), 656 (M$^+$−2Br); Anal. Calcd for $C_{42}H_{36}N_6O_2Br_2$: C, 61.76; H, 4.41; N, 10.29; Found: C, 61.65; H, 4.32; N, 10.45.

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