Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6127–6130

Synthesis and structural characterization of chiral dicationic imidazolophanes

Perumal Rajakumar,* Subramaniyan Selvam and Manickam Dhanasekaran

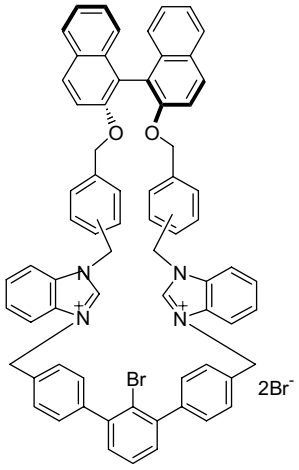
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, Tamil Nadu, India

Received 17 March 2005; revised 19 June 2005; accepted 29 June 2005
Available online 19 July 2005

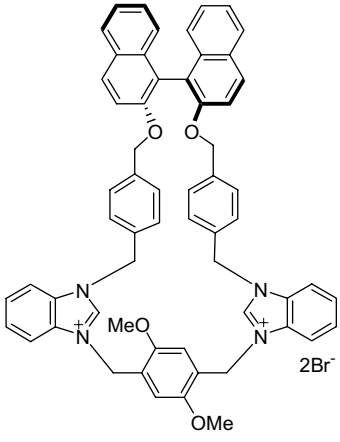
Abstract—Various chiral dicationic benzimidazolophanes were obtained from optically pure (*S*)-BINOL, benzimidazole and a suitable aryl alkyl dibromide.

Molecular recognition of anionic guests[1,2] by synthetic cationic receptors[3] is an area of interest at present. Developing cationic receptor systems, which are capable of recognizing, sensing and transporting anionic species is an interesting and challenging problem. Due to their structural versatility and opportunities for synthetic modifications, cyclophanes have received much attention in the areas of host-guest complexation, molecular self-assembly and specific receptor activity. Imidazole-based dicationic cyclophanes have been used for the synthesis of carbenoid complexes,[4,5] a silver complex,[6] and also exhibit interesting conformational behaviour.[7] Chiralophane[8,9] and dicationic cyclophanes such as imidazolophanes,[10,11] imidazoliophanes,[12] triazolophanes,[13–15] tetracationic receptors[16] and viologen based cyclophanes[17,18] have been reported in the literature. However, to the best of our knowledge the synthesis of chiral cationic imidazolophanes remains to be explored. Hence, we report the synthesis and structural characterization of the (*S*)-BINOL-based chiral imidazolophanes **1a**,**b**, **2** and **3a**–**d**. Furthermore, the synthesis of cyclophanes **1a** and **1b** with large cavities is of interest as they may form complexes with large chiral anions.

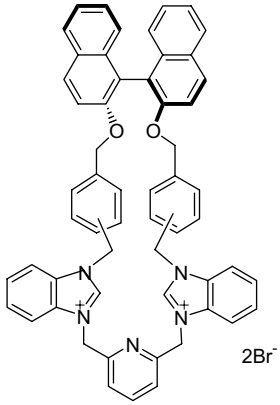
The synthesis of dicationic chiral receptors **1a** and **1b** can be achieved either from (*S*)-BINOL and capping with *m*-terphenyl dibromide or from *m*-terphenyl dibromide and capping with (*S*)-BINOL. Syntheses of all the cationic chiralophanes depicted above have been carried out by both routes. Reaction of (*S*)-BINOL with



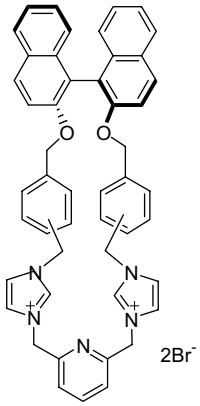
1a *para*
1b *meta*



2



3a *para*
3b *meta*

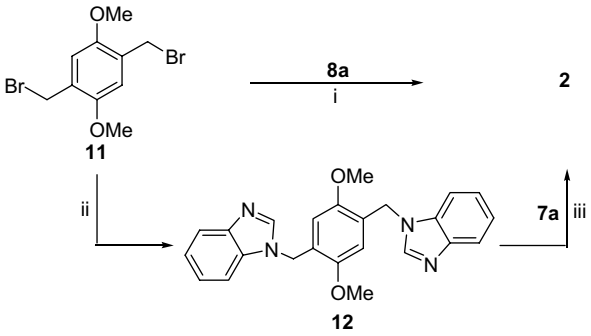


3c *para*
3d *meta*

Keywords: Chiral dicationic benzimidazolophanes; Chiral pyridinoimidazolophanes.
* Corresponding author. Tel.: +91 4422351269; fax: +91 44 22352494; e-mail: perumalrajakumar@hotmail.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.159

2.1 equiv of 4-carbethoxybenzyl bromide gave the diester **5a**, which on reduction with $LiAlH_4$ followed by reaction with PBr_3 gave the dibromide **7a** in a 72% yield. Reaction of the dibromide **7a** with 2.1 equiv of benzimidazole in CH_3CN in the presence of 25% aq NaOH for 2 days afforded the precyclophane **8a** in 78% yield, which was characterized by spectral and analytical data.[19] Coupling of the precyclophane **8a** with 2′-bromo-4,4″bis(bromomethyl)-1,1′:3′1″-terphenyl (**9**) gave the cyclophane **1a** along with other inseparable products and hence the synthesis of cyclophane **1a** in pure form could not be achieved by this method. In another approach, the *m*-terphenyl dibromide **9** was reacted with 2.1 equiv of benzimidazole in the presence of 25% aq NaOH in CH_3CN to give the bridged benzimidazole derivative **10**.

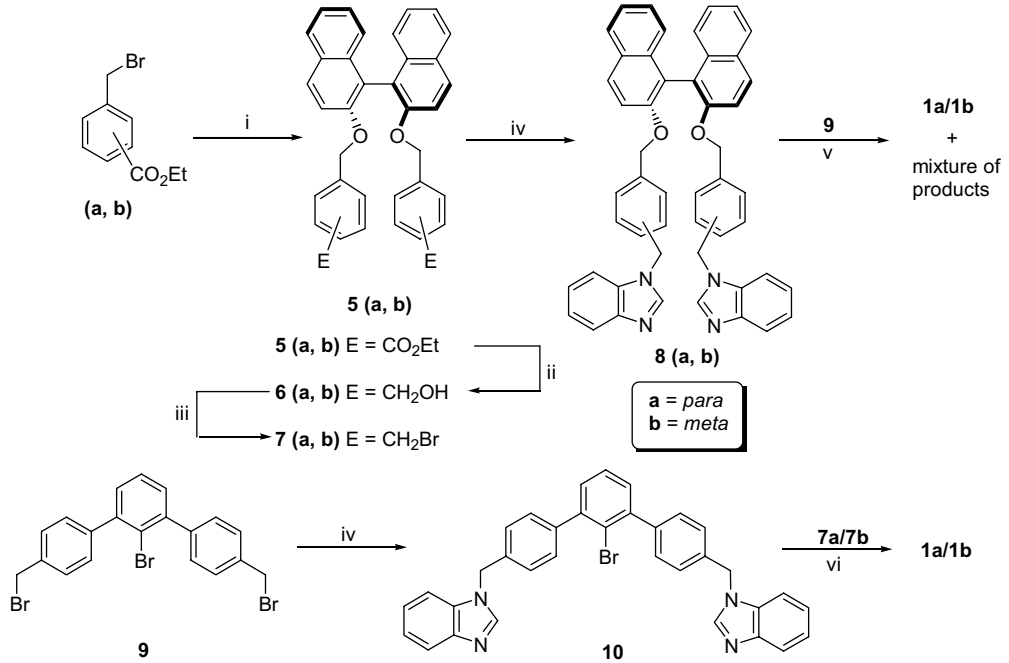


Scheme 2. Reagents and conditions: (i) CH_3CN, reflux, 5 days, 60%; (ii) 2.1 eq benzimidazole, aq. NaOH (25%), CH_3CN, rt, 2 days, 70%; (iii) CH_3CN, reflux, 5 days, 58%.

The reaction of **10** with 1 equiv of the dibromide **7a** in CH_3CN under reflux for 5 days afforded the cyclophane **1a** in a 72% yield. The ^1H NMR spectrum of **1a**[20] displayed *N*-methylene protons as singlets at δ 5.72 and δ 5.87 and *O*-methylene protons as doublets at δ 5.02 and δ 5.11, in addition to 39 aromatic protons. The methine proton of the imidazole ring system in receptor **1a** appeared at δ 10.21. A similar sequence using 3-carbethoxybenzyl bromide gave the cyclophane **1b** with a 69% yield for the last step (Scheme 1).

Synthesis of the benzimidazolophane **2** is of interest due to the presence of the 1,4-dimethoxy-2,5-xylenyl capping unit. Atropisomerism might be observed for such a capping unit. The synthesis of cyclophane **2** was carried out by two methods. Reaction of the precyclophane **8a** with 1 equiv of 1,4-bis(bromomethyl)-2,5-dimethoxybenzene (**11**)[21] in CH_3CN afforded the dicationic cyclophane **2** in 60% yield. In another approach, the dibromide **11** was reacted with 2.1 equiv of benzimidazole in the presence of aq. NaOH (25%) to give the bisbenzimidazole derivative **12**, which on further reaction with the dibromide **7a** in CH_3CN, gave the dicationic cyclophane **2** in 58% yield. Hence, benzimidazolophane **2** was synthesized by both routes with comparable yields (Scheme 2).

The ^1H NMR spectrum of benzimidazolophane **2**[22] displayed the methoxy protons as a six proton singlet at δ 3.80 and doublets for the *O*-methylene protons at δ 4.90 and at δ 5.02. The *N*-methylene protons appeared as doublets at δ 5.78 and δ 5.86 integrating for four protons and a four proton singlet at δ 5.73 in addition to 30 aromatic protons. It is noteworthy to mention that the methine proton of the benzimidazole ring system appeared as a singlet at δ 10.78.



Scheme 1. Reagents and conditions: (i) (*S*)-BINOL, K_2CO_3, DMF, 60 °C, 2 days, **5a** (71%), **5b** (65%); (ii) $LiAlH_4$, THF, 6 h, **6a** (85%), **6b** (75%); (iii) PBr_3, CH_2Cl_2, 0 °C, 4 h, **7a** (72%), **7b** (82%); (iv) 2.1 equiv benzimidazole, aq. NaOH (25%), CH_3CN, rt, 2 days, **8a** (78%), **8b** (72%) and **10** (70%); (v) CH_3CN, reflux, 5 days; (vi) CH_3CN, reflux, 5 days, **1a** (72%), **1b** (69%).

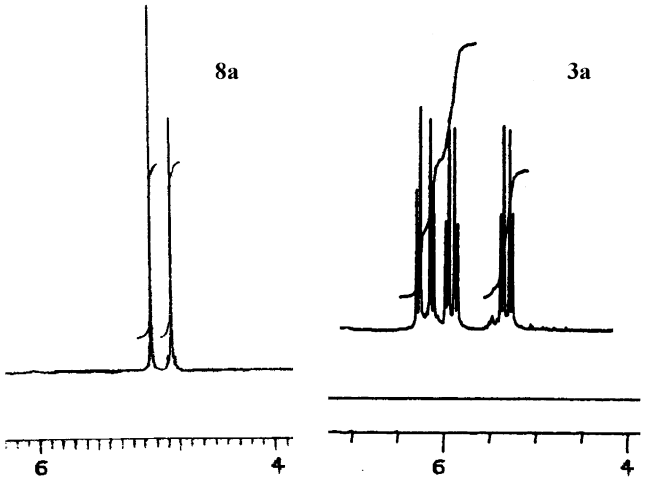
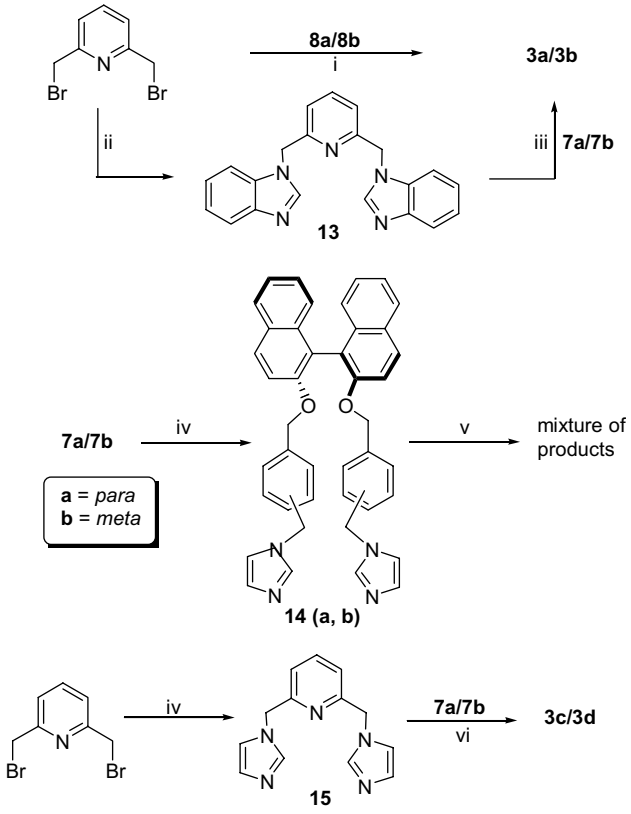


Figure 1. ^{1}H NMR spectrum (methylene protons) of precyclophane **8a** and cyclophane **3a**.

Cyclophanes, which have both electron rich and electron deficient centres, are called self-complementary cyclophanes. Dicationic cyclophanes of the type **3a–d** have a chiral segment as well as a base segment, that is, a pyridine unit in addition to the dicationic centre. Such cyclophanes may be used as chiral receptors for chiral anionic guests as well as chiral carboxylic acids, hence the synthesis of dicationic chiralophanes **3a–d** is of interest. Cyclophanes **3a** and **3b** were synthesized by two approaches.

In the first synthetic approach, precyclophane **8a**, synthesized as reported earlier (Scheme 1) was coupled with 1 equiv of 2,6-bis(bromomethyl)pyridine to give the benzimidazolophane **3a**[23] in 65% yield. It is noteworthy that in the ^{1}H NMR the methylene protons in precyclophane **8a** appeared as two singlets at δ 4.85 and δ 5.03, whereas after coupling with 2,6-bis(bromomethyl)pyridine, the methylene protons in cyclophane **3a** appeared as three pairs of doublets at δ 5.26, 5.35, 5.86, 5.95, 6.12 and 6.26 (Fig. 1). Application of a similar sequence using 3-carbethoxybenzyl bromide gave the cyclophane **3b**[24] in a 55% overall yield. Alternatively, 2,6-bis(bromomethyl) pyridine was reacted with 2.1 equiv of benzimidazole and the resulting bis-benzimidazole **13** was reacted with dibromides **7a/b** to give the cyclophanes **3a/b** in 60% and 54% yields, respectively. Hence, cyclophanes **3a** and **3b** could be synthesized by both approaches with comparable yields (Scheme 3).

Similarly, precyclophanes **14a** and **14b** were synthesized from the dibromides **7a/b** and imidazole. However, the sequence with the precyclophane **14a** and 2,6-bis-(bromomethyl)pyridine did not afford the cyclophane **3c**. The coupling reaction of the precyclophane **14a/b** with 2,6-bis(bromomethyl)pyridine gave a mixture of products. Hence, **3c**[25] and **3d** were synthesized by the coupling reaction of precyclophane **15** with 1 equiv of dibromide **7a/b**. Precyclophane **15** was easily obtained by the alkylation of 2.1 equiv of imidazole with 2,6-bis(bromomethyl)pyridine (Scheme 3). Synthesis of



Scheme 3. Reagents and conditions: (i) CH_3CN, reflux, 5 days, **3a** (65%), **3b** (55%); (ii) 2.1 equiv benzimidazole, aq. NaOH (25%), CH_3CN, rt, 2 d, (62%); (iii) CH_3CN, reflux, 5 days, **3a** (60%), **3b** (54%); (iv) 2.1 equiv imidazole, aq. NaOH (25%), CH_3CN, rt, 2 days, **14a** (18%), **14b** (20%) and **15** (37%); (v) 2,6-bis(bromomethyl)pyridine, CH_3CN, reflux, 5 days, (vi) CH_3CN, reflux, 5 days, **3c** (52%) **3d** (48%).

other related cationic chiralophanes and their complexation with chiral anions are underway.

Acknowledgements

The authors thank DST, India, for financial assistance and RSIC, CDRI Lucknow, for FAB-MS spectra. M.D. thanks CSIR for providing a SRF.

References and notes

1. Ramos, S.; Alcade, E.; Doddi, G.; Mencarelli, P.; Perez-Garcia, L. *J. Org. Chem.* **2002**, *67*, 8463–8468.
2. Ihm, H.; Yun, S.; Kim, H. G.; Kim, J. K.; Kim, K. S. *Org. Lett.* **2002**, *17*, 2897–2900.
3. Yuan, Y.; Gao, G.; Jiang, Z. L.; You, J. S.; Zhou, Z. Y.; Yuan, D. Q.; Xie, R. G. *Tetrahedron* **2002**, *58*, 8993–8999.
4. Simons, S. R.; Garrison, J. C.; Kofron, W. G.; Tessier, C. A.; Youngs, W. J. *Tetrahedron Lett.* **2002**, *43*, 3423–3425.
5. Baker, M. V.; Skelton, B. W.; White, A. H.; Williams, W. C. *Organometallics* **2002**, *21*, 2674–2678.
6. Garrison, J. C.; Simons, R. S.; Kofron, W. G.; Tessier, C. A.; Youngs, W. J. *Chem. Commun.* **2001**, 1780–1781.
7. Baker, M. V.; Bosnich, M. J.; Brown, D. H.; Byrne, L. T.; Hesler, V. J.; Skelton, B. W.; White, A. H.; Williams, W. C. *J. Org. Chem.* **2004**, *69*, 7640–7652.

8. Castro, P.; Diederich, F. *Tetrahedron Lett.* **1991**, *32*, 6277–6280.
9. Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **2002**, *43*, 1909–1913.
10. Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **1997**, *38*, 5323–5326.
11. Rajakumar, P.; Dhanasekaran, M. *Tetrahedron* **2002**, *58*, 1355–1359.
12. Alcade, E.; Alvarez-Rua, C.; Garcia-Granda, S.; Garcia-Rodriguez, E.; Jesquida, N.; Perez-Garcia, L. *Chem. Commun.* **1999**, 295–296.
13. Rajakumar, P.; Murali, V. *Tetrahedron* **2000**, *56*, 7995–7999.
14. Rajakumar, P.; Murali, V.; Ganesan, K. *Synth. Commun.* **2003**, *33*, 4191–4198.
15. Rajakumar, P.; Murali, V. *Chem. Commun.* **2001**, 2710–2711.
16. Rajakumar, P.; Srinivasan, K. *Eur. J. Org. Chem.* **2003**, 1277–1284.
17. Deng, N.; Marwaha, V. R.; Garcia, M. E.; Benesi, A.; Mallouk, T. E. *Tetrahedron Lett.* **1995**, *36*, 7599–7602.
18. Garcia, M. E.; Gavin, J. A.; Deng, N.; Andrievsky, A. A.; Mallouk, T. E. *Tetrahedron Lett.* **1996**, *37*, 8313–8316.
19. Precyclophane **8a**: yield 78%; $[\alpha]_D^{30}$ −42.77, (*c* 0.01, $CHCl_3$); mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (s, 4H); 5.03 (s, 4H); 6.73 (s, 8H); 7.07–7.20 (m, 12H); 7.25 (d, 2H, $J = 9.0$ Hz); 7.71–7.76 (m, 6H); 7.80 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR: (100 MHz, $CDCl_3$); δ 48.5, 70.7, 110.1, 115.9, 120.3, 120.7, 122.4, 123.1, 123.9, 125.5, 126.4, 127.0, 127.3, 127.9, 129.4, 129.5, 133.8, 134.1, 134.4, 137.7, 143.1, 143.7, 153.9; *m*/*z* (FAB-MS) 726 (M^+). Elemental Anal. Calcd for $C_{50}H_{38}N_4O_2$: C, 82.62; H, 5.27; N, 7.71. Found: C, 82.42; H, 5.18, N, 7.90.
20. Cyclophane **1a**: yield 72%; $[\alpha]_D^{30}$ −4.27, (*c* 0.01, DMSO); mp 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.02 (d, 2H, $J = 13.1$ Hz); 5.11 (d, 2H, $J = 13.1$ Hz); 5.72 (s, 4H); 5.87 (s, 4H); 6.87 (d, 4H, $J = 8.1$ Hz); 6.96 (d, 2H, $J = 8.4$ Hz); 7.12–7.16 (m, 2H); 7.20–7.23 (m, 5H); 7.38–7.43 (m, 6H); 7.47–7.51 (m, 6H); 7.56 (t, 2H, $J = 7.4$ Hz); 7.64–7.71 (m, 4H); 7.79 (d, 2H, $J = 8.0$ Hz); 7.93 (d, 2H, $J = 9.1$ Hz); 8.03–8.05 (m, 2H); 8.18–8.20 (m, 2H); 10.21 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 50.2, 50.3, 80.2, 114.9, 116.3, 120.0, 124.4, 125.4, 127.2, 128.0, 128.1, 128.5, 128.7, 128.8, 129.6, 129.9, 130.8, 131.5, 131.7, 131.9, 134.1, 134.2, 134.8, 138.9, 142.5, 143.3, 143.5, 154.2; *m*/*z* (FAB-MS) 1141 (M^+−Br); 1061 (M^+−2Br). Elemental Anal. Calcd for $C_{70}H_{53}N_4O_2Br_3$: C, 68.81; H, 4.37; N, 4.59. Found: C, 68.66; H, 4.28; N, 4.61.
21. Nair, M. S.; Sudhir, U.; Joly, S.; Rath, N. P. *Tetrahedron* **1999**, *55*, 7653.
22. Cyclophane **2**: yield 60%; $[\alpha]_D^{30}$ −55.82, (*c* 0.01, DMSO); mp 160 °C; ^{1}H NMR: (400 MHz, DMSO-d_6): δ 3.80 (s, 6H); 4.90 (d, 2H, $J = 13.0$ Hz); 5.02 (d, 2H, $J = 13.0$ Hz); 5.73 (s, 4H); 5.78 (d, 2H, $J = 15.0$ Hz); 5.86 (d, 2H, $J = 15.0$ Hz); 7.01 (d, 4H, $J = 8.0$ Hz); 7.14–7.21 (m, 8H); 7.26–7.34 (m, 6H); 7.54–7.56 (m, 2H); 7.64–7.66 (m, 2H); 7.83 (d, 2H, $J = 7.9$ Hz); 7.87 (d, 4H, $J = 9.0$ Hz); 8.09 (d, 2H, $J = 8.3$ Hz); 10.78 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 46.8, 50.4, 56.9, 71.1, 113.2, 114.3, 116.2, 116.3, 120.7, 121.9, 124.0, 125.5, 126.6, 127.4, 127.5, 128.2, 128.3, 129.7, 131.3, 131.9, 132.5, 134.2, 139.0, 142.0, 152.0, 154.3; *m*/*z* (FAB-MS) 970; (M^+−Br); 890 (M^+−2Br). Elemental Anal. Calcd for $C_{60}H_{50}N_4O_4Br_2$: C, 68.58; H, 4.80; N, 5.33. Found: C, 68.48; H, 4.65; N, 5.28.
23. Cyclophane **3a**: yield 65%; $[\alpha]_D^{30}$ −96.17, (*c* 0.01, DMSO); mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.26 (d, 2H, $J = 13.6$ Hz); 5.35 (d, 2H, $J = 13.6$ Hz); 5.86 (d, 2H, $J = 15.6$ Hz); 5.95 (d, 2H, $J = 15.6$ Hz); 6.12 (d, 2H, $J = 15.6$ Hz); 6.26 (d, 2H, $J = 15.6$ Hz); 7.32 (s, 2H); 7.36 (d, 4H, $J = 7.8$ Hz); 7.59 (d, 4H, $J = 8.2$ Hz); 7.63 (s, 2H); 7.67 (d, 2H, $J = 8.8$ Hz); 7.71 (d, 2H, $J = 8.3$ Hz); 7.93–7.99 (m, 6H); 8.12 (d, 2H, $J = 7.8$ Hz); 8.31 (t, 4H, $J = 8.8$ Hz); 8.37–8.41 (m, 3H); 10.18 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 49.4, 50.8, 68.8, 113.5, 115.3, 119.2, 123.2, 123.5, 124.5, 126.4, 126.5, 126.7, 127.3, 127.8, 128.7, 129.2, 130.5, 131.1, 132.8, 133.5, 138.1, 142.8, 151.7, 153.1; *m*/*z* (FAB-MS) 911 (M^+−Br); 831 (M^+−2Br). Elemental Anal. Calcd for $C_{57}H_{45}N_5O_2Br_2$: C, 69.03, H, 4.57; N, 7.06. Found: C, 69.28; H, 4.69; N, 7.20.
24. Cyclophane **3b**: yield 55%; $[\alpha]_D^{30}$ −89.36, (*c* 0.01, DMSO); mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.00 (d, 2H, $J = 13.2$ Hz); 5.10 (d, 2H, $J = 15.4$ Hz); 5.18 (d, 2H, $J = 13.2$ Hz); 5.33 (d, 2H, $J = 15.4$ Hz); 5.83 (d, 2H, $J = 16.0$ Hz); 5.86 (d, 2H, $J = 16.0$ Hz); 6.83 (d, 2H, $J = 7.4$ Hz); 6.92 (t, 2H, $J = 8.0$ Hz); 6.98 (d, 2H, $J = 8.6$ Hz); 7.03 (d, 2H, $J = 7.4$ Hz); 7.18 (s, 2H); 7.22–7.25 (m, 2H); 7.29 (t, 2H, $J = 8.0$ Hz); 7.32–7.36 (m, 2H); 7.45 (t, 2H, $J = 8.0$ Hz); 7.51 (d, 2H, $J = 9.1$ Hz); 7.53 (d, 2H, $J = 8.6$ Hz); 7.57 (d, 2H, $J = 8.0$ Hz); 7.71 (d, 2H, $J = 7.4$ Hz); 7.94 (t, 4H, $J = 9.1$ Hz); 8.01 (t, 1H, $J = 7.4$ Hz); 9.88 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 49.5, 50.6, 69.6, 113.6, 115.7, 119.4, 122.8, 123.7, 124.5, 126.4, 126.6, 126.8, 126.9, 128.0, 128.9, 128.9, 129.2, 130.2, 131.1, 140.0, 133.4, 138.3, 142.7, 152.6, 153.4; *m*/*z* (FAB-MS) 911 (M^+−Br), 831 (M^+−2Br). Elemental Anal. Calcd for $C_{57}H_{45}N_5O_2Br_2$: C, 69.03; H, 4.57; N, 7.06. Found: C, 69.28; H, 4.69; N, 7.20.
25. Cyclophane **3c**: yield: 68%; $[\alpha]_D^{30}$ −146.30, (*c* 0.01, DMSO); mp 198–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.05 (d, 2H, $J = 13.7$ Hz); 5.27 (d, 2H, $J = 13.7$ Hz); 5.31 (s, 4H); 5.48 (d, 2H, $J = 15.6$ Hz); 5.60 (d, 2H, $J = 15.6$ Hz); 7.00 (d, 2H, $J = 17.7$ Hz); 7.08 (d, 4H, $J = 8.0$ Hz); 7.16 (d, 4H, $J = 8.0$ Hz); 7.26 (t, 2H, $J = 7.3$ Hz); 7.35 (t, 2H, $J = 8.0$ Hz); 7.53 (s, 2H); 7.59–7.64 (m, 6H); 8.00–8.02 (m, 3H); 8.05 (d, 2H, $J = 9.1$ Hz); 9.20 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 51.5, 52.6, 68.8, 115.2, 119.2, 121.8, 122.6, 123.6, 124.6, 126.5, 127.2, 128.0, 128.3, 128.8, 129.4, 133.4, 133.6, 136.6, 138.2, 138.8, 153.1, 153.2; *m*/*z* (FAB-MS) 811 (M^+−Br); 731 (M^+−2Br). Elemental Anal. Calcd for $C_{49}H_{41}N_5O_2Br_2$: C, 66.00; H, 4.63; N, 7.85. Found: C, 65.90; H, 4.54; N, 7.93.