N-Tosylated Polyaza[n](1,4)naphthalenophanes. Synthesis and Conformational Studies

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N-Tosylated polyaza[n](1,4)naphthalenophanes containing from 3 to 6 nitrogen atoms and from 9 to 18 atoms in the saturated bridge can be prepared in high yields from 1,4-bis(bromomethyl)-naphthalene and the appropriate N-tosylated polyamine chains. NMR data and molecular mechanics calculations suggest the prevalence of conformations in which the polyamine bridge is located above the aromatic ring. Variable-temperature NMR experiments show that internal rotation of the aromatic ring is not allowed, on the NMR time scale, even at 180 °C for naphthalenophanes having chain lengths of 12 or less. For naphthalenophanes with chain lengths of 14 or 15 atoms, the rotational barrier is on the order of 12 kcal mol^{-1} as calculated from VT-NMR data.

The design of synthetic receptors containing well-defined structural features is of great interest.[1] Recently, we have prepared and studied several polyaza[n]paracyclophanes as water-soluble receptors having some interesting properties, especially in their interaction with metal ions.[2] One of the most attractive structural features of those compounds is the potential convergence of the aromatic ring and the nitrogen donor atoms in the cavity. Because of the nature of donor atoms, these receptors seem appropriate to study the interaction of π-systems with transition metal cations as well as with anionic guests in aqueous solutions. Preorganization plays an essential role in host–guest chemistry.[3,4] In this sense, it is important to study in more detail the conformational mobility of these systems to gain further insight into the assumption that polyaza[n]paracyclophanes exist most of the time in conformations with the polyamine bridge arching above the face of the aromatic ring presumably due to the restricted rotation of the aromatic ring and the hindered ability of the polyamine bridge to move past the edge of the aromatic ring. In general, unsymmetrically substituted [n]paracyclophanes should have nonequivalent benzilic methylene protons that should allow NMR analysis of the restricted rotation of the aromatic ring provided that the rate is slow enough on the NMR time scale.[5,6] Simple paracyclophanes having ansa chain lengths of 10–12 experience such aromatic ring rotations, on the same time scale, at temperatures of 60–160 °C.[6f] However, the limiting chain length has been shown to be dependent on the nature of the chain. Thus, for instance, for paracyclophanes in which the benzene ring contains substituents in the 2 and 5 positions, different limiting chain lengths are observed when the chain is formed via two amide or two ester linkages.[6a-e] Polyaza[n]paracyclophanes reported to date are symmetrical and, accordingly, not appropriate for such a study. However, a simple way to overcome this difficulty is to substitute the 1,4-phenylene subunit by a 1,4-naphthalene moiety.[7-12] Thus, equilibration of two equivalent rotational conformers (Scheme 1) can be easily monitored through the temperature-dependent study of the ^{1}H NMR signals of the naphthylic protons.

Values for the energy of activation for this process can provide a point of reference for the related polyaza[n]-paracyclophanes which cannot be so studied. We report on the synthesis and conformational studies of several N-tosylated polyaza[n](1,4)naphthalenophanes (1–6), containing from three to six nitrogen atoms and having

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Scheme 1

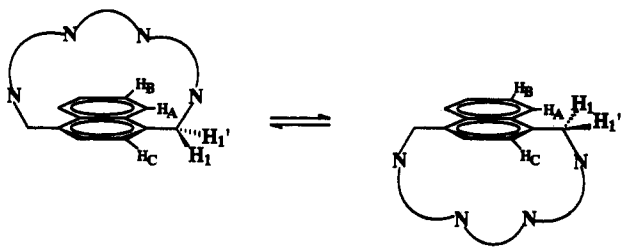


Table 1. Isolated Yields of Tosylated Polyaza[n](1,4)naphthalenophanes

compound	reaction time (h)	yield (%)[a]	mp (°C)
1	17	98	226–227
2	30	82	277–280
3	20	92	152–153
4	30	75	262–263
5	7	87	184–185
6	18	36	250–252

[a] Isolated yields after chromatographic purification.

chain lengths ranging from 9 to 18 atoms which present diastereomeric proton environments suitable for such studies.

Naphthalenophanes, and specially (1,4)naphthalenophanes have received much attention in recent years.[7-13] A limited number of crown ethers containing (1,4)- and (1,5)naphthalene fragments have been prepared[9] in order to study the interaction of the π-system of the naphthalene with complexed alkali metal cations.[10] Receptors based on the structure of [n,n](1,4)naphthalenophanes containing oxygen atoms and acetylenic spacers have been developed by Whitlock,[11] and several dithia[n,n](1,4)-naphthalenometacyclophanes have been recently studied.[12] The preparation of 2,6,10-tris(trifluoroacetyl)-2,6,10-triaza[11](2,6)naphthalenophane in 26% yield was described by Sutherland.[13] However, polyaza[n](1,4)-naphthalenophanes have not been reported. Synthesis of compounds 1–6 was carried out according to the general method recently developed for the preparation of N-tosylated polyaza[n]paracyclophanes,[2a] and described, as a general procedure, for the preparation of compound 2 in the Experimental Section. The method consists of dropwise addition of a solution of 1,4-bis(bromomethyl)-naphthalene in CH_3CN to a refluxing suspension containing the respective tosylated polyamine dissolved in CH_3CN and K_2CO_3 as the base. Elution chromatographic purification of the crude product on silica gel with CH_2Cl_2/AcOEt (97/3, v/v) as eluent afforded the pure N-tosylated polyaza[n](1,4)naphthalenophanes in 40–95% yields (Table 1). The products appeared as single spots by TLC in a number of solvents. Additional purification was carried out by crystallization from toluene. Yields are much higher than those previously reported for the [11](2,6)naphthalenophane[13] and even higher than yields obtaned for the preparation of related [n]paracyclophanes.[2a] This is noteworthy, especially for the [9]- and the [18](1,4)-naphthalenophanes 1 and 6. These results seems to further support the important role that steric factors play in such cyclizations.

The aliphatic region of the ^1H NMR spectra of naphthalenophanes 1–6 taken at 22 °C is shown in Figure 1. The assignment of the ^1H NMR signals was done by a

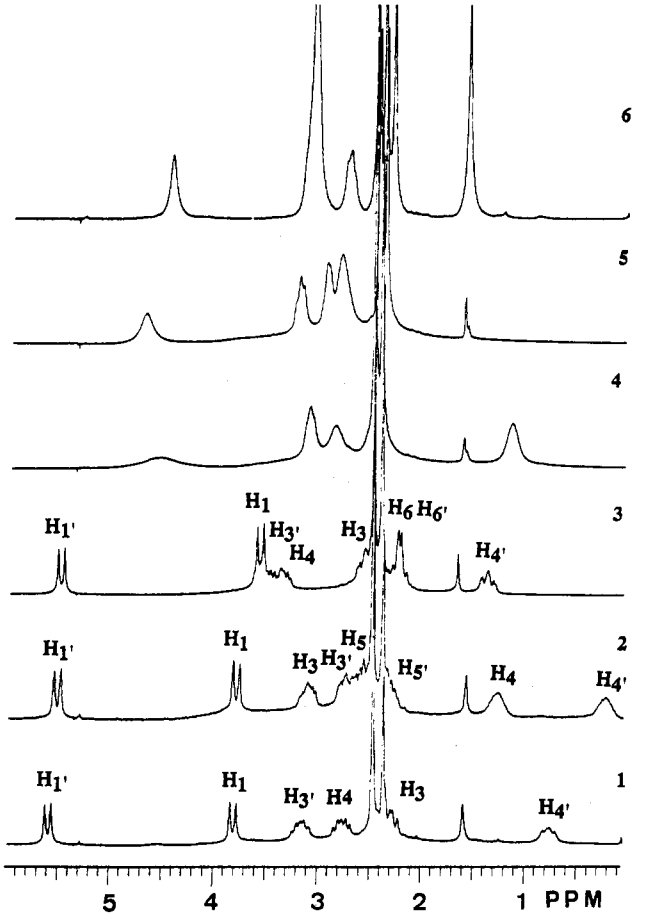
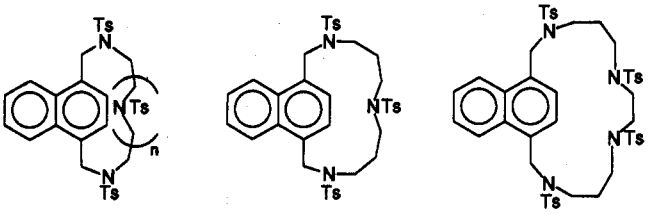


Figure 1. Aliphatic region of the ^1H NMR spectra for compounds 1–6, taken in $CDCl_3$ at 22 °C.

Chart 1



1: n = 1; 3: n = 2 2 4

5: n = 3; 6: n = 4

combination of 2D NMR techniques (^1H–^1H and ^1H–^{13}C COSY) and NOE experiments as well as considering analogous data for related naphthalenophanes.[8,9] The chemical shifts of the naphthalenic protons do not greatly differ from those of (1,4)dialkylnaphthalenes and appear as two multiplets centered at 8.3–8.6 (H_A) and 7.6 ppm (H_B) and a singlet at ca 7.3 ppm (H_C). Analysis of the ^1H NMR signals in the aliphatic region gives experimental evidence of the extent of equilibration of the rotational conformations of compounds 1–6 (Scheme 1). Naphthylic protons (H_1 and $H_{1'}$) provide the most convenient NMR signals for the study of this process. In the left-side conformer of Scheme 1, one proton on each naphthylic position ($H_{1'}$) is directed toward the peri proton (H_A), the other (H_1) being directed out away from the naphthalene system. This should be reflected in an appreciable chemical shift difference between H_1 and $H_{1'}$.[8,9] Internal rotation of the aromatic ring would interchange the situation of each hydrogen atom. If this conformational

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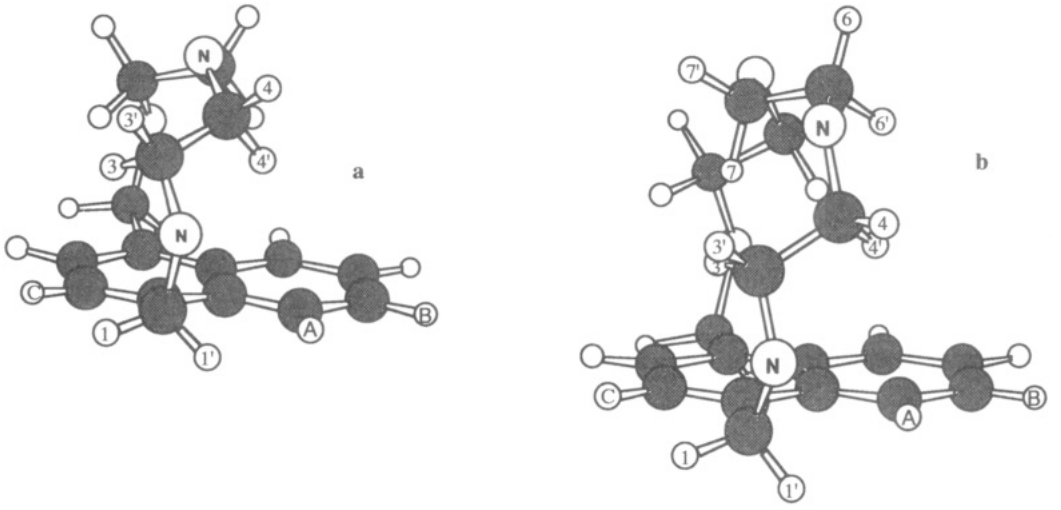

Figure 2. Calculated structures for the lowest energy conformers[15] of **1** (a) and **3** (b) in chloroform. Tosyl groups have been omitted for clarity.

equilibrium is slow on the NMR time scale, an AB quartet should be observed, but only an A_2 singlet if the rate for this process is fast enough on the same time scale.

The ^1H NMR spectrum of the pertosylated 2,5,8,11,14,17-hexaaza[18](1,4)naphthalenophane **6** displays a sharp singlet at 4.46 ppm in the naphthylic region, showing that equilibration is very fast at room temperature. For the [14]- and [15]naphthalenophanes **4** and **5**, broad singlets appear at 4.5 and 4.7 ppm respectively, indicating that coalescence temperature is close to room temperature, especially in the case of **4**. For the smaller naphthalenophanes **1–3**, an AB quartet (J = 12 Hz) is observed in the naphthylic region indicative of slow equilibration of these cyclophanes at room temperature. Additionally, for **1–3**, the geminal protons in the bridges also become nonequivalent and separate signals can be observed for each geminal partner. This agrees with the prevalence of conformations in which the polyamine chain is over the face of the naphthalene ring. The bridge protons which are located above the unsubstituted ring of the naphthalene exhibit clear upfield shifts relative to analogous protons in N-tosylated polyaza[n]paracyclophanes.[2a] The converse is apparent for the protons directing toward the periphery of the aromatic ring as has already been reported in [6](1,4)naphthalenophane.[8a]

In order to better understand the conformational preferences of naphthalenophanes **1–6**, we carried out molecular mechanics calculations.[14] We applied the torsional Monte Carlo method exploited by the BATCHMIN V3.5 molecular mechanics program, as a part of the MACROMODEL package.[15] In the conformational searches of compounds **1–6** in chloroform, a high number of conformers were found within 1–2 kcal mol^{-1} of the minimum energy assignment. However, for the smaller naphthalenophanes **1-3**, all those low-energy conformers have essentially the same arrangement of the naphthalene groups and polyamine bridges but differ in the tosyl group orientations. For all of the (1,4)naphthalenophanes studied, the lowest energy conformer corresponds to one for which the polyamine bridge is situated above the aromatic ring (see Figure 2).

Thus, molecular mechanics calculations are in agreement with the interpretation of the NMR data of compounds **1–3**. As can be observed in Figure 2a, the structure of the [9]naphthalenophane **1** shows the presence of a proton $H_{4'}$, and the equivalent $H_{6'}$, which is located at a short distance (from the molecular mechanics calcuations, a distance of 2.6 Å can be estimated) above the unsubstituted naphthalene ring.[16] Accordingly, $H_{4'}$ is observed at 0.8 ppm while the other proton at C-4 (H_4) appears 2 ppm downfield. A smaller shielding is observed for H_3 (δ = 2.4 ppm), which is located above the plane of the substituted naphthalene ring (a distance of 2.3 Å is derived from the molecular mechanics calculations), but on the periphery of the aromatic system. NOE experiments[17] also support the structure depicted in Figure 2a. Irradiation of $H_{4'}$ produced a clear enhancement of the H_A signal in agreement with the 3.0-Å distance predicted from molecular mechanics. Enhancements are also observed from the $H_{1'}$ resonance to H_A (calcd distance 2.1 Å) and from the H_1 resonance to H_C (calcd distance 2.3 Å) and H_3 (calcd distance 3.0 Å). Additional NOE enhancements are observed from H_4 and $H_{3'}$ to the ortho protons of the tosyl group located on the center of the bridge, and from H_1, $H_{1'}$, and $H_{3'}$ to the ortho hydrogen atoms of the other tosyl groups.

For compound **2**, containing two propylenediamine subunits in the chain, the most noticeable feature in the calculated structure is the prediction that higher shielding is to be expected on one of the protons of the central methylene in the propylenic unit. This is confirmed by the ^1H NMR spectrum in which one of the signals appears at 0.25 and the other at 1.3 ppm. Shielding effects and chemical shift differences are smaller for the protons of the other methylene groups, resonances being observed at 2.6 and 2.4 ppm for protons at C-3 and 3.2 and 2.8 ppm at C-5. For the [12](1,4)naphthalenophane **3**, the higher shielding of $H_{4'}$ ($\delta H_{4'}$ = 1.4, δH_4 = 3.4) is consistent with the structure of the low-energy conformer displayed in Figure 2b as well as the NOE enhancement from this proton to H_A, calculated distance 2.8 Å. As can be seen in Figure 2b protons $H_{6'}$ and $H_{7'}$, as well as H_6 and H_7, are not located in equivalent positions. Nevertheless, in the other possible

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Table 2. Temperature-Dependent ^1H NMR Spectral Data and Thermodynamic and Kinetic Parameters[a]

compound	^1H NMR probe	coales temp ± 3 °K	$\Delta\nu \pm 2$ Hz, (temp)	$k_c \pm 5$ s^{-1}	$\Delta G_c^{\ddagger} \pm 0.3$ kcal/mol
4	H_1	273	330 (238)	733	12.4
4	H_4	258	107 (238)	238	12.2
5	H_1	263	224 (238)	498	12.4

[a] $\Delta\nu$: frequency separation for the observed signals with the temperature at which it was measured. No appreciable changes in $\Delta\nu$ were observed below the indicated temperature. k_c: exchange rate constant at coalescence temperature. $\Delta G_c^{\ddagger}$: free energy of activation for the exchange process at coalescence temperature.

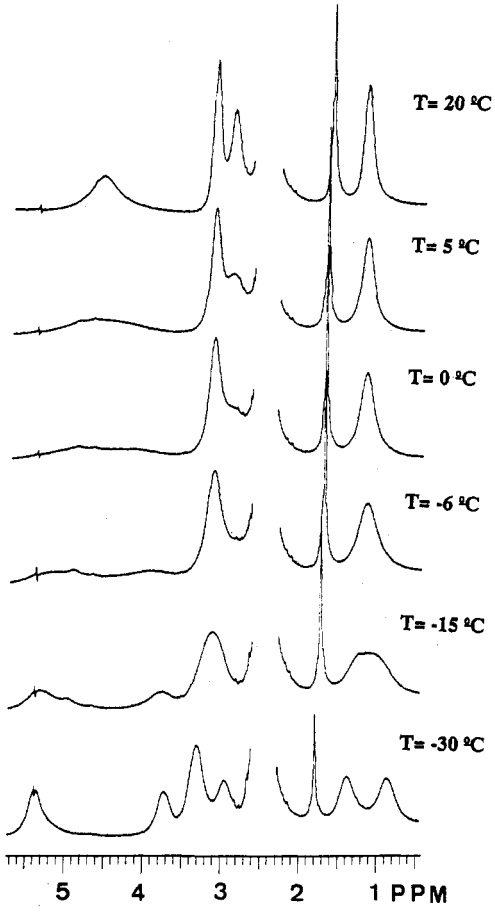

Figure 3. Variable-temperature ^1H NMR spectra of [14]naphthalenophane 4, aliphatic region.

conformation of the same energy reached by the flipping of the chain, these protons exchange their positions. The result is that protons on the central ethylenic subunit in 3 are located above the naphthalene ring but, in both cases, at average mean distances of ca. 4.5–4.6 Å from the aromatic system. This explains their lower shielding as well as the similar shifts observed ($\Delta\delta < 0.1$ ppm).

Variable temperature NMR spectra of naphthalenophanes 4 and 5 were measured in order to determine the free energy barriers for the equilibration of the rotational conformations (see Scheme 1). Results are summarized in Table 2 and variations in the aliphatic region of the ^1H NMR with the temperature for compounds 4 and 5 are shown in Figures 3 and 4. For the smaller naphthalenophanes 1–3, the AB quartet in the naphthylic region showed a slight broadening but no sign of coalescence even when the spectra were measured at 180 °C in DMSO-d_6, demanding a free energy of conformational equilibration greater than 21–22 kcal mol^{-1}. For naphthalenophanes 4

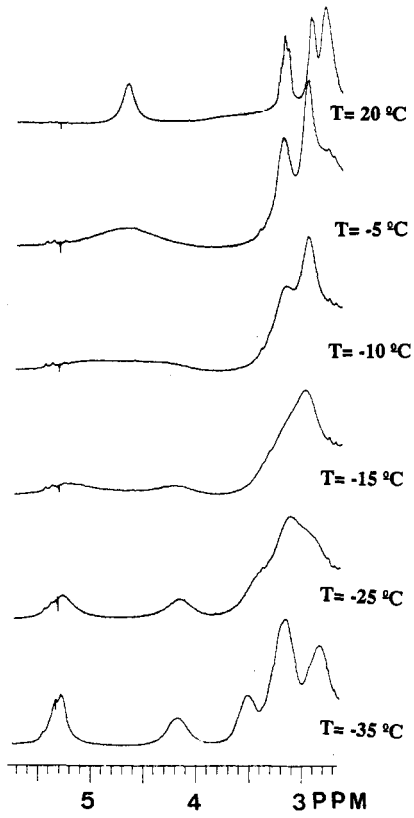

Figure 4. Variable-temperature ^1H NMR spectra of [15](1,4)-naphthalenophane 5, aliphatic region.

and 5 in $CDCl_3$, at low temperatures the naphthylic singlets separated into two broadened signals located at ca. 5.3 and 3.7 ppm for 4 and 5.3 and 4.2 ppm for 5. For compound 6, solubility problems precluded achieving the low temperatures required for VT-NMR analysis. Variable temperature ^1H NMR spectra gave coalescence temperatures of 0 °C and −10 °C for 4 and 5, respectively, for the naphthylic signals. The signals for the other protons in the chain also exhibited temperature dependence, although in nearly all cases these are difficult to interpret because of overlapping and excessive signal broadening. However, the signals corresponding to the central methylene group of the propylene subunit of [14]naphthalenophane 4 were amenable to analysis. At 22 °C the geminal protons appear as a multiplet centered at 1.15 ppm, while at −20 °C two separate signals at ca. 0.85 and 1.35 ppm were observed. The coalescence temperature was, in this case, −15 °C. As can be seen in Table 2, the values for the free energies of activation obtained using naphthylic and propylenic protons in 4 as different probes are in good agreement. Note further the small differences in energy barriers for 4 and 5. A similar small energy difference has also been observed for [10]- and [11]paracyclophanes with a bromomethyl substituent in the ring.[6f] The value of the rotational barrier is much higher than that reported for the analogous process in a 1,5-naphtho-22-crown-6 (6.3 kcal mol^{-1}).[9] The conformational interconversion depicted in Scheme 1 requires ring inversion by rotation about two C_{sp3}–C_{sp2} bonds and nitrogen inversion. This likely occurs through a stepwise mechanism accompanied by chain reorganization during different steps.[18–21] The presence of the bulky tosyl groups may be a dominant factor in determining the exact value of the interconversion barrier.[21]

In summary, NMR data and molecular mechanics calculations support, for naphthalenophanes 1–6, the prevalence of conformations in which the polyamine chain is located above the aromatic ring. Naphthalenophanes 1–3 which have less than 12 atoms in the chain show no sign of the internal rotation of the aromatic ring, even at high temperatures, on the NMR time scale.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively, in $CDCl_3$.

***N,N',N''*-Tritosyl-2,6,10-triaza[11](1,4)naphthalenecyclophane (2).** Pertosylated 1,5,9-triazanonane[2a] (2.0 g, 3.4 mmol) and K_2CO_3 were suspended in refluxing CH_3CN (75 mL). To this mixture, a solution of 1,4-bis(bromomethyl)naphthalene[9] (1.1 g, 3.4 mmol) in CH_3CN (150 mL) was added dropwise. After the addition was complete, the suspension was refluxed for 17 h and then filtered. The solution was vacuum evaporated to dryness to yield the crude product which was purified by elution column chromatography on silica gel (CH_2Cl_2/AcOEt 97/3) to afford pure **2** as a white solid (2.1 g, 82%): mp 277- 280 °C; IR (KBr) 2925, 1598, 1466, 1338, 1158, 660 cm^{-1}; ^1H NMR δ 0.23 (m, 2 H), 1.28 (m, 2 H), 2.30 (m, 2 H), 2.40 (s, 3 H), 2.49 (s, 6 H), 2.60 (m, 2 H), 2.70 (m, 2 H), 3.10 (m, 2 H), 3.80 (d, J = 12.7 Hz, 2 H), 5.52 (d, J = 12.7 Hz, 2 H), 7.23 (d, J = 9.9 Hz, 2 H), 7.4 (m, 8 H), 7.65 (dd, J_1 = 6.2 Hz, J_2 = 2.9 Hz, 2 H), 7.80 (d, J = 8.1 Hz, 4 H), 8.47 (dd, J_1 = 6.2 Hz, J_2 = 2.9 Hz, 2 H); ^{13}C NMR δ 21.5, 21.6, 30.9, 46.9, 48.7, 53.1, 125.1, 126.9, 127.3, 127.4, 128.0, 129.7, 130.0, 132.3, 133.2, 134.7, 135.5, 143.3, 143.7; MS m/z (FAB) 746 ([M + H]$^+$). Anal. Calcd for $C_{39}H_{43}N_3S_3O_6$: C, 62.8; H, 5.8; N, 5.6; S, 12.9. Found: C, 62.4; H, 5.8; N, 5.6; S, 12.6.

***N,N',N''*-Tritosyl-2,5,8-triaza[9](1,4)naphthalenecyclophane (1):** 98% yield; mp 226–227 °C; ^1H NMR δ 0.78 (m, 2 H), 2.30 (m, 2 H), 2.38 (s, 3 H), 2.48 (s, 6 H), 2.77 (m, 2 H), 3.16 (m, 2 H), 3.82 (d, J = 11.7 Hz, 2 H), 5.60 (d, J = 11.7 Hz, 2 H), 7.25 (d, J = 8.1 Hz, 2 H), 7.35 (s, 2 H), 7.40 (d, J = 8.1 Hz, 4 H), 7.52 (d, J = 8.1 Hz, 2 H), 7.65 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 4 H), 8.30 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 2 H); ^{13}C NMR δ 21.5, 21.6, 46.4, 52.1, 52.8, 125.0, 127.3, 127.4 127.8, 129.6, 129.7, 130.0, 132.5, 134.6, 143.7; MS m/z (FAB) 718 ([M + H]$^+$). Anal. Calcd for $C_{37}H_{39}N_3S_3O_6$: C, 61.9; H, 5.5; N, 5.8; S, 13.4. Found: C, 61.4; H, 5.5; N, 5.8; S, 13.6.

***N,N',N'',N'''*-Tetratosyl-2,5,8,11-tetraaza[12](1,4)naphthalenecyclophane (3):** 92% yield; mp 153–154 °C; ^1H NMR δ 1.37 (m, 2 H), 2.24 (m, 4 H), 2.41 (s, 6 H), 2.49 (s, 6 H), 2.57 (m, 2 H), 3.3 (m, 2 H), 3.4 (m, 2 H), 3.58 (d, J = 12.6 Hz, 2 H), 5.50 (d, J = 12.6 Hz, 2 H), 7.18 (s, 2 H), 7.25 (d, J = 8.7 Hz, 4 H), 7.42 (d, J = 8.7 Hz, 4 H), 7.6 (m, 6 H), 7.85 (d, J = 8.7 Hz, 4 H), 8.50 (dd, J_1 = 6.8 Hz, J_2 = 3.4 Hz, 2 H); ^{13}C NMR δ 21.5, 21.6, 46.8, 50.2, 53.5, 125.2, 127.3, 127.7, 127.9, 130.0, 132.2, 132.5, 133.3, 135.5, 143.6, 144.1; MS m/z (FAB) 915 ([M + H]$^+$). Anal. Calcd for $C_{46}H_{50}N_4S_4O_8$: C, 60.4; H, 5.5; N, 6.1; S, 14.0. Found: C, 60.1; H, 5.5; N, 6.1; S, 13.6.

***N,N',N'',N'''*-Tetratosyl-2,6,9,13-tetraaza[14](1,4)naphthalenecyclophane (4):** 75% yield; mp 262–263 °C; ^1H NMR δ 1.16 (m, 4 H), 2.43 (s, 6 H), 2.49 (s, 10 H), 2.86 (m, 4 H), 3.1 (m, 4 H), 4.57 (s, 4 H), 7.24 (s, 2 H), 7.28 (d, J = 8.1 Hz, 4 H), 7.42 (d, J = 8.1 Hz, 4 H), 7.5–7.6 (m, 6 H), 7.82 (d, J = 8.1 Hz, 4 H), 8.55 (dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, 2 H); ^{13}C NMR δ 21.5, 21.6, 29.1, 46.9, 47.5, 47.6, 53.6, 124.9, 127.2, 127.3, 127.5, 129.7, 130.0 132.4, 134.3, 135.5, 143.4, 143.8; MS m/z (FAB) 943 ([M + M]$^+$). Anal. Calcd for $C_{48}H_{54}N_4S_4O_8$: C, 61.1; H, 5.8; N, 5.9; S, 13.6. Found: C, 60.6; H, 5.7; N, 5.9; S, 13.5.

***N,N',N'',N''',N''''*-Pentatosyl-2,5,8,11,14-pentaaza[15](1,4)naphthalenecyclophane (5):** 87% yield; mp 184–185 °C; ^1H NMR δ 2.40 (s, 6 H), 2.44 (s, 3 H), 2.47 (s, 6 H), 2.82 (m, 8 H), 2.95 (m, 4 H), 3.22 (m, 4 H), 4.71 (s, 4 H), 7.20 (s, 2 H), 7.25–7.30 (m, 10 H), 7.5–7.7 (m, 8 H), 7.82 (d, J = 7.3 Hz, 4 H), 8.25 (dd, J_1 = 5.9 Hz, J_2 = 3.1 Hz, 2 H); ^{13}C NMR δ 22.1, 47.3, 50.6, 52.2, 52.6, 125.2, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 130.2, 130.4, 130.5, 132.1, 132.5, 134.7, 135.2, 144.3, 144.4, 144.7; MS m/z (FAB) 1112 ([M + H]$^+$). Anal. Calcd for $C_{55}H_{61}N_5S_5O_{10}$: C, 59.4; H, 5.5; N, 6.3; S, 14.4. Found: C, 60.1; H, 5.7; N, 6.1; S, 14.0.

***N,N',N'',N''',N'''',N''''*-Hexatosyl-2,5,8,11,14,17-hexaaza[18](1,4)naphthalenecyclophane (6):** yield 35%; mp 250–252 °C; ^1H NMR δ 2.33 (s, 6 H), 2.42 (s, 6 H), 2.50 (s, 6 H), 2.70 (m, 4 H), 3.10 (m, 16 H), 4.46 (s, 4 H), 6.59 (s, 2 H), 7.1–7.2 (m, 12 H), 7.44 (d, J = 8.1 Hz, 4 H), 7.68 (dd, J_1 = 6.6 Hz, J_2 = 3.5 Hz, 2 H), 7.75 (d, J = 8.2 Hz, 4 H), 7.92 (d, J = 8.3 Hz, 4 H), 8.46 (dd, J_1 = 6.6 Hz, J_2 = 3.5 Hz, 2 H); ^{13}C NMR δ 21.5, 46.8, 49.7, 50.0, 50.8, 51.6, 53.0, 125.2, 126.8, 127.0, 127.3, 127.8, 128.1, 129.7, 129.8, 130.0, 132.3, 132.8, 133.8, 134.1, 134.6, 143.6, 143.9; MS m/z (FAB) 1309 ([M + H]$^+$). Anal. Calcd for $C_{64}H_{72}N_6S_6O_{12}$: C, 58.7; H, 5.5; N, 6.4; S, 14.7. Found: C, 59.1; H, 5.7; N, 6.2; S, 14.4.

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