An Efficient Synthesis of Polyaza[n]paracyclophanes

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The design of polyammonium receptors containing structural features that impart high selectivity in the recognition of different guests in aqueous solution has received much attention in the past several years.[1,2] The design of the receptors has been especially important in the study of the molecular recognition of anions, where structural factors have been shown to play significant roles besides simple charge–charge interactions.[3,6] Aromatic subunits are often introduced as integral parts of the receptors. A large number of macrocyclic or macropolycyclic polyammonium receptors containing two or more 1,4-benzo subunits have been synthesized.[7-12] Polyammonium receptors containing three or more 1,4-benzo moieties have most often been used as water-soluble receptors with hydrophobic cavities that can also interact with guests by π-stacking or π-cation interactions.[8,9,11,13] In some instances, two or three unfunctionalized *p*-phenylene subunits have been introduced as spacers to link two polyamine chains or two polyaza-crown structures to form ditopic macrocycles or cryptands. Functionalization of the aromatic rings can impart interesting properties to the receptors.[12] However, [*n*]paracyclophanes containing O, N, or S donor atoms in the chain have been, up to now, less studied despite their potentially attractive structural features.[14] In these compounds, the aromatic ring and the donor atoms could converge in the cavity, and the aromatic moiety could act as a rigid spacer between some of the donor atoms in the chain. Recently we have found[15] that the 2,6,9,13-tetraaza[14]paracyclophane shows some interesting properties as a receptor, especially in its interaction with metal ions. For the preparation of this receptor, the reaction of tosylated tetraamine **4** (R = Ts, R′ = H) with 1,4-bis(bromomethyl)benzene in the presence of metal carbonates in DMF, one of the most common modifications of the method of Richman and Atkins,[16-19] afforded the expected product in low yields, but the yields improved when the reaction was carried out in refluxing CH_3CN. Herein, we report this general method for the simple and efficient preparation of polyaza[*n*]paracyclophanes, as well as the scope and limitations of the method. Several novel polyaza[*n*]paracyclophanes have been synthesized in this way.

In the original procedure of Richman and Atkins, polyazamacrocycles were synthesized by cyclization of the disodium salt of a N-tosylated polyamine and a compound containing two tosyl leaving groups in DMF.[16,17] In a related method, the reactions of a tosyl amide monosodium salt with bis(halomethyl)benzenes were reported for the preparation of several [3.3]cyclophanes.[20] *In situ* deprotonation of the ditosylamine with Cs_2CO_3 in DMF and cyclization with various dibromides or dimesylates were especially effective for the synthesis of large-sized macrocycles.[18a] A similar procedure has been used, for instance, to prepare several cupped azacyclophanes from a tetrakis(bromomethyl) *m*-terphenyl.[21] Alternatively, the use of K_2CO_3 in DMF has been proven to be very useful

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Chart I

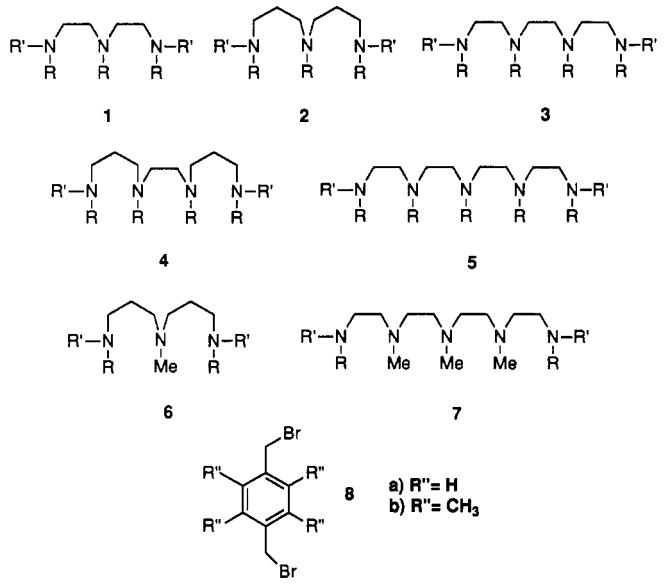
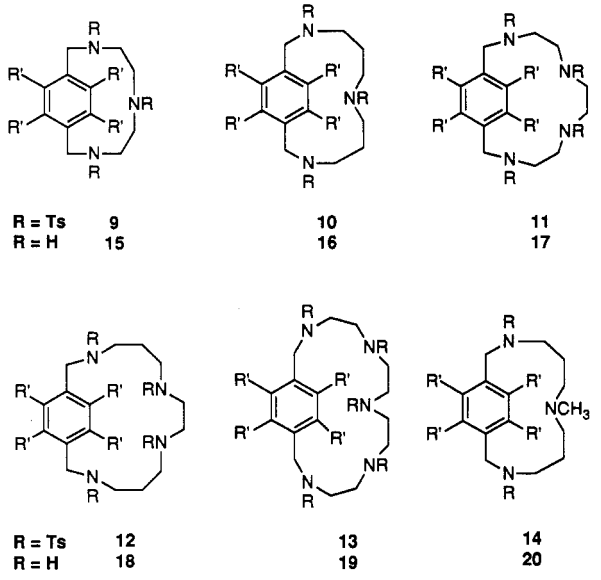


Chart II



for the preparation of small- and medium-sized polyaza macrocycles including two polyaza 1,2-benzo macrocycles.[19]

None of the former methods was effective for the preparation of polyaza[*n*]paracyclophanes. However, under our conditions, the expected cyclophanes **9–14** (R′ = H or CH_3) could be isolated in 40–96% yields after purification by chromatography or crystallization (see Table I). For the preparation of starting tosylated polyamine chains **1–6** (R = Ts, R′ = H), polyamines **1–6** (R = R′ = H) were treated with TsCl in the presence of NaOH in a H_2O/THF mixture. Amines **1–6** (R = R′ = H) were commercially available, and compound **7** (R = H, R′ = Ts) was prepared according to a previously reported procedure.[22] In a typical cyclization reaction (Scheme I) a solution of the bis(halomethyl)benzene **8** in CH_3CN was

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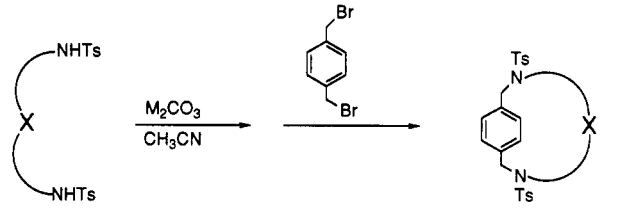
Table I. Isolated Yields of Tosylated Polyaza[*n*]paracyclophanes

entry	bis(bromomethyl) compound	tosylated polyamine[a]	base	reaction time (h)	product	yield[b] (%)
1	**8a**	**1**	K_2CO_3	24	**9a**	40
2	**8a**	**2**	Na_2CO_3	24	**10a**	10
3	**8a**	**2**	K_2CO_3	24	**10a**	71
4	**8a**	**2**	Cs_2CO_3	17	**10a**	74
5	**8a**	**3**	K_2CO_3	24	**11a**	77
6	**8a**	**4**	Na_2CO_3	24	**12a**	39
7	**8a**	**4**	Na_2CO_3	120	**12a**	70
8	**8a**	**4**	K_2CO_3	24	**12a**	81
9	**8a**	**4**	K_2CO_3	31	**12a**	90
10	**8a**	**4**	Cs_2CO_3	19	**12a**	96
11	**8a**	**5**	K_2CO_3	24	**13a**	86
12	**8b**	**2**	K_2CO_3	24	**10b**	81
13	**8b**	**3**	K_2CO_3	24	**11b**	71
14	**8b**	**4**	K_2CO_3	24	**12b**	76
15	**8b**	**6**	K_2CO_3	24	**14b**	50

[a] See Chart I, R = Ts, R′ = H. [b] Isolated yields after chromatographic purification.

Scheme I



X = N-Tosylated polyamine chain

added dropwise over a period of 1–4 h to a refluxing suspension containing the tosylated amine (**1–7**, R = Ts, R′ = H) dissolved in CH_3CN and potassium or cesium carbonate as the base. Refluxing was continued for 20-30 h, and, after a simple workup including chromatographic purification, the pure N-tosylated polyaza[*n*]paracyclophanes **9–14** were obtained in the yields indicated in Table I. All compounds showed the expected spectroscopic properties and satisfactory elemental analyses and mass spectra and appeared as single spots by TLC in a number of solvents. The corresponding 2:2 cyclization products seemed to be present in very minor amounts in some crudes, but the main side products were oligomeric or polymeric materials.

As can be observed from the data in Table I, the cyclization step was very efficient for a variety of polyamine chains. Comparable results were also obtained when bis(bromomethyl)benzene (**8a**) was replaced with bis(chloromethyl)- or bis(bromomethyl) durene (**8b**). Polyaza[*n*]paracyclophanes ranging from [9]paracyclophane (i.e., **9**) to [15]paracyclophane (i.e., **13**) could thus be obtained. The [9]paracyclophane structure seemed to be the smallest ring that could be prepared by the present method, and yields for macrocycle **9** were slightly lower than for larger sizes. In agreement with this size limitation, the reaction with *N,N′*-bis(tolylsulfonyl)ethylenediamine gave only oligomeric materials along with minor amounts of 2:2 and higher cyclization products.

The high yields obtained in this cyclization step are remarkable. They are much higher than the 7–10% yield reported for the preparation of related crown ethers[14] or the 26% yield described for a [11](2,6)-naphthalenophane[10e] and are comparable with results described

for the preparation of polyaza macrocycles containing 1,2-benzo subunits.[19] A number of diaza[n]paracyclophanes have been synthesized by the high dilution method from α,ω-diamines and the dichlorides of diacids containing the 1,4-phenylene structure, but reported yields are usually below 10%.[23] Clearly, once the first N–C bond is formed, the first order intramolecular pathway leading to the cyclic compounds **9–14** is favored over the second-order pathways leading to oligomeric and polymeric materials or other cyclic compounds. In fact, this reaction was not drastically affected by dilution conditions: in general, changing the concentration of reactants from 10^{-3} to 10^{-2} M did not significantly affect the final yield, and the yield was only slightly decreased by addition of the dibromide all in one portion. Compound **12a** was the only isolated product (>80% yield) even when the stoichiometry of the amine and the dibromide was changed from the 1:1 ratio to a 1:5 ratio.

A classical template effect, where the chain containing the heteroatoms wraps around the cation, thus preorganizing the transition state for cyclization, does not seem probable in our case. Such an effect should be much more effective for macrocycles with 1,2-benzo subunits than for those with 1,4-benzo subunits. The study of the effect of the cation on the yield also suggests that the template effect is not operating. K_2CO_3 and Cs_2CO_3 always give the best results for the cyclizations, even if the paracyclophanes obtained are of very different sizes. The nature of the cation seems to affect the rate of the reaction more than it does the final yield. Thus, for instance, the yield of **12a** is very similar with K_2CO_3 and Cs_2CO_3, with only a 2-fold increase in the reaction time required for the former (entries 9 and 10, Table I). For the same macrocycle, the use of the sodium salt produces a comparable yield after a reaction time of 120 h compared to 24 h for the potassium salt (entries 7 and 8, Table I). Analogous situations are found for the other macrocycles (see, for instance, entries 3 and 4 in Table I). Therefore, K_2CO_3 seems to be the most useful base when both efficiency and cost are considered. These results can be better understood in terms of the different basicities of the carbonates.[18] Since the cesium salt is the most basic, the anion is formed very easily, and the reaction proceeds faster. For the lithium salt, the basicity is so low that no reaction is observed in any case. For lithium, unchanged starting materials are the main products recovered after the workup, and a similar situation is observed when Na_2CO_3 is used as the base. The differing solubilities of the salts formed and ion pair effects also have to be taken into account.[18] The importance of these factors is reinforced by the dramatic effect observed when the solvent is changed from DMF to CH_3CN. Most likely, conformational factors should assist the favorable organization of the transition state leading to the macrocycle. The presence of the bulky tosyl groups seems to be very important in this respect. Thus, no cyclization products were formed when untosylated polyamines were allowed to react with bis(halomethyl)benzenes **8**. In the Richman and Atkins procedure and other related procedures, the tosyl group is introduced not only to protect the nitrogen atoms but also to increase the acidity of the terminal N–H bonds. However, it is not likely that the lower acidity of the N–H bond is responsible for the failure of this cyclization. Metal carbonate-mediated reaction of bis-secondary amines with different dihalides in acetonitrile has become a standard method for the preparation of functionalized polyaza macrocycles;[24] the reactions of diaza crown ethers with bis(halomethyl)-arenes under similar conditions have been used for the synthesis of tricyclic receptors;[10d] and, in some instances, cyclizations of primary diamines and dihalides have been reported.[25] In our case, however, steric and conformational factors associated with the tosyl groups prevail. The importance of steric factors is clearly shown by the fact that only oligomeric or polymeric materials were formed in the reaction of ditosyl N-methylated polyamines **6** and **7** (R = Ts, R′ = H) with bis(bromomethyl)benzene (**8a**). An interesting difference was observed, however, when bis(bromomethyl)durene (**8b**) was used instead of **8a**. In this case, [11]paracyclophane **14b** (R = Ts, R′ = CH_3) was obtained in 50% yield, a fact which could also support the important role that steric factors play in this reaction.

Detosylation of macrocycles **9a–13a** (R = Ts, R′ = H) to give polyaza[n]paracyclophanes **15a–19a** (R = R′ = H) was effected with HBr/AcOH/PhOH.[26] The final macrocyclic amines were isolated in 80–90% yields and were 90–95% pure in most cases. Purification by silica gel chromatography with MeOH/THF/NH_3 as the eluent afforded pure **15a–19a**, but the yield for this step was decreased to 40–60%. This method could not be applied to durene derivatives. The higher lability of the benzylic C–N bonds in these compounds precludes the use of strongly acidic conditions because detosylation is accompanied by benzylic cleavage leading to the salts of the starting polyamines as the main products. For those tetramethyl[n]paracyclophanes, detosylation was best carried out with sodium amalgam in buffered methanolic solution.[18a,19,27] Because of the low solubility of these tosylated macrocycles in MeOH, THF had to be added in some cases. Yields of 40–50% were obtained for the pure compounds.

The ^1H NMR spectra of polyaza[n]paracyclophanes **9–20** show the expected shielding effect of the aromatic ring on the central protons of the chain. The value of the observed upfield shift is, in general, in good agreement with the values reported for other paracyclophanes of similar size.[23,28] Thus, for **11a** the central ethylene is shifted upfield (ca. 0.45 ppm) relative to the other ethylenic protons and, even more significantly, relative to the position of the singlet in open chain analogue **3** (R = Ts, R′ = Bn). In free amine **17a**, the singlet is shifted ca. 0.4 and 0.7 ppm from the other ethylenic protons. Shifts are smaller for larger cyclophanes, and the singlet of the ethylenic group in **12** appears ca. 0.3 ppm upfield relative to the singlet of related **4** (R = Ts, R′ = Bn). In smaller cyclophanes shielding affects most of the protons in the

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polyamine chain, but significant differences in the chemical shift are observed for the nonequivalent hydrogens. For instance, for **16a** and **16b**, the two N-bound methylene groups of the propylene subunit are separated by ca. 0.3 and 0.2 ppm, respectively. For smaller cyclophane **9a**, an upfield shift of 0.6 ppm is observed for the central methylene relative to open chain compound **1** (R = Ts, R′ = Bn), and, for untosylated **15a**, the difference in chemical shift between both methylenes is also 0.6 ppm. Comparison of these data with those obtained for the 2:2 cyclization product formed from *N,N′*-ditosylethylenediamine is also interesting in this respect. For this macrocycle, the ethylenic protons are not appreciably shielded, but shielding is observed for the aromatic protons, as has been described for related [*n.n*]paracyclophanes.[20]

In summary, we have demonstrated that the present method allows the simple and efficient synthesis of a broad range of polyaza[*n*]paracyclophanes. Study of the potential uses of these compounds as hosts for different species and further structural modifications for specific applications in this field are in progress.

Experimental Section

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

***N,N′,N″*-Tritosyl-1,5,9-triazanonane (2, R = Ts, R′ = H).** To a solution of **2** (R = R′ = H) (6.5 g, 0.05 mol) and NaOH (10 g, 0.20 mol) in 100 mL of H_2O at 60 °C was added dropwise tosyl chloride (28.6 g, 0.15 mol) in THF. After addition was complete, stirring and heating was continued for 4 h. The organic layer was vacuum evaporated and the residue suspended in hot ethanol for several hours to give the tosylated polyamine as a white solid (24 g, 0.04 mol, 80%). Further purification can be achieved by column chromatography on silica (CH_2Cl_2 or CH_2Cl_2/AcOEt): mp 116–119 °C; ^{1}H NMR δ 1.7 (q, 4 H), 2.4 (s, 6 H), 2.9 (t, 4 H), 3.1 (t, 4 H), 5.2 (s, 2 H), 7.2 (d, 6 H), 7.6 and 7.7 (dd, 6 H). ^{13}C NMR δ 29, 40, 47, 127, 129.6, 129.7, 132.2, 136.5, 143.3, 143.5. Anal. Calcd for $C_{27}H_{35}N_3S_3O_6$: C, 54.6; H, 5.9; N, 7.1. Found: C, 55.0; H, 5.8; N, 6.9.

***N,N′,N″*-Tritosyl-1,4,7-triazaheptane (1, R = Ts, R′ = H):** 82% yield; mp 179–180 °C (lit.[17c,29] 177 °C); ^{1}H NMR δ 2.40 (s, 9 H), 3.16 (m, 8 H), 5.3 (m, 2 H), 7.3 (m, 6 H), 7.62 (d, 2 H), 7.76 (d, 4 H); ^{13}C NMR δ 21.8, 42.7, 50.8, 127.6, 127.8, 130.3, 130.5, 135.2, 137.1, 144.1, 144.6.

***N,N′,N″,N‴*-Tetratosyl-1,4,7,10-tetraazadecane (3, R = Ts, R′ = H):** 65% yield; mp 215–217 °C (lit.[29] 215–219 °C); ^{1}H NMR δ 2.42 (s, 6 H), 2.45 (s, 6 H), 3.20 (m, 8 H), 3.43 (s, 4 H), 5.45 (t, 2 H), 7.27 (s, 4 H), 7.33 (t, 8 H), 7.73 (t, 8 H), 7.77 (d, 4 H); ^{13}C NMR δ 21.5, 43.7, 50.9, 127.1, 127.4, 128.4, 129.8, 129.9, 131.0, 133.6, 134.6.

***N,N′,N″,N‴*-Tetratosyl-1,5,8,12-tetraazadodecane (4, R = Ts, R′ = H):** 70% yield; mp 145 °C; ^{1}H NMR δ 1.79 (q, 4 H), 2.41 (s, 6 H), 2.44 (s, 6 H), 3.00 (m, 4 H), 3.15 (t, 4 H), 5.27 (t, 2 H), 7.2–7.3 (m, 8 H), 7.6–7.7 (m, 8 H); ^{13}C NMR δ 21.5, 29.1, 48.1, 48.2, 54.7, 127.2, 127.3, 129.1, 129.8, 129.9, 134.9, 135.2, 136.7, 143.5, 143.6. Anal. Calcd for $C_{36}H_{46}N_4S_4O_8$: C, 54.7; H, 5.9; N, 7.1. Found: C, 55.1; H, 5.7; N, 7.1.

***N,N′,N″,N‴,N⁗*-Pentatosyl-1,4,7,10,13-pentaazatridecane (5, R = Ts, R′ = H):** 37% yield; mp 173–175 °C (lit.[30] 173–175 °C); ^{1}H NMR δ 2.40 (s, 6 H), 2.43 (s, 6 H), 2.46 (s, 3 H), 3.18 (s, 8 H), 3.37 (s, 8 H), 5.5 (broad, 2 H), 7.3 (m, 10 H), 7.7 (m, 10 H); ^{13}C NMR δ 21.5, 43.2, 49.8, 50.3, 50.5, 127.1, 127.4, 129.7, 129.8, 129.9, 130.0, 134.7, 136.5, 143.4, 143.8, 143.9.

1,9-Ditosyl-5-methyl-1,5,9-triazanonane (6, R = Ts, R′ = H): 58% yield as a waxy solid; ^{1}H NMR δ 1.70 (m, 4 H), 2.22 (s, 3 H), 2.40 (s, 6 H), 2.51 (t, 4 H), 2.96 (t, 4 H), 7.28 (d, 4 H), 7.73 (d, 4 H); ^{13}C NMR δ 21.9, 25.4, 41.8, 45.6, 56.2, 127.6, 130.1, 137.3, 143.7. Anal. Calcd for $C_{21}H_{31}N_3S_2O_4$: C, 55.6; H, 6.9; N, 9.3. Found: C, 55.9; H, 7.0; N, 9.1.

***N,N′,N″,N‴*-Tetratosyl-2,5,8,11-tetraaza[12]paracyclophane (11a).** Tosylated amine **3** (R = Ts, R′ = H) (1.0 g, 1.3 mmol) and K_2CO_3 were suspended in refluxing CH_3CN (50 mL). To this mixture, a solution of 1,4-bis(bromomethyl)-benzene (0.35 g, 1.3 mmol) in CH_3CN (50 mL) was added dropwise. After the addition was complete, the suspension was refluxed for 18 h and then filtered. The solution was vacuum evaporated to dryness to yield the crude product, which was purified by column chromatography on silica (CH_2Cl_2/AcOEt 99/1) to afford pure **11a** as a white solid (0.86 g, 1.0 mmol, 77%): mp 274–278 °C; IR (KBr) 3045, 2928, 2866, 1591, 1482, 1439, 1334, 1152 cm^{-1}; ^{1}H NMR δ 2.45 (s, 6 H), 2.47 (s, 6 H), 2.50 (s, 4 H), 2.85 (m, 4 H), 2.91 (m, 4 H), 4.14 (s, 4 H), 7.32 (d, *J* = 8 Hz, 4 H), 7.33 (s, 4 H), 7.39 (d, *J* = 8 Hz, 4 H), 7.68 (d, *J* = 8 Hz, 4 H), 7.78 (d, *J* = 8 Hz, 4 H); ^{13}C NMR δ 21.6, 47.4, 48.2, 50.2, 54.3, 127.4, 127.5, 129.9, 133.8, 135.4, 136.1, 143.7, 144.0; MS *m/z* (FAB) 865 ([M + H]$^+$). Anal. Calcd for $C_{42}H_{48}N_4O_8S_4$: C, 58.3; H, 5.6; N, 6.5. Found: C, 58.2; H, 5.7; N, 6.3.

***N,N′,N″*-Tritosyl-2,5,8-triaza[9]paracyclophane (9a):** 40% yield; mp 274–276 °C; ^{1}H NMR δ 2.44 (s, 3 H), 2.46 (s, 6 H), 2.52 (m, 8 H), 4.25 (s, 4 H), 7.26–7.40 (m, 10 H), 7.63–7.69 (m, 6 H); ^{13}C NMR δ 21.5, 44.4, 48.0, 54.0, 127.1, 127.2, 129.8, 129.9, 132.2, 134.9, 136.0, 137.2, 143.3, 143.7; MS *m/z* (FAB) 668 ([M + H]$^+$). Anal. Calcd for $C_{33}H_{37}N_3O_6S_3$: C, 59.3; H, 5.6; N, 6.3. Found: C, 59.6; H, 5.7; N, 6.1.

***N,N′,N″*-Tritosyl-2,6,10-triaza[11]paracyclophane (10a):** 71% yield; mp 323–327 °C; ^{1}H NMR δ 1.19 (m, 4 H), 2.42 (s, 3 H), 2.47 (s, 6 H), 2.71 (m, 4 H), 3.03 (t, *J* = 7 Hz, 4 H), 4.20 (s, 4 H), 7.31–7.37 (m, 6 H), 7.43 (s, 4 H), 7.60 (d, *J* = 8 Hz, 2 H), 7.71 (d, *J* = 8 Hz, 4 H); ^{13}C NMR δ 21.5, 30.1, 48.2, 48.5, 54.7, 126.8, 127.1, 129.8, 129.9, 135.6, 136.2, 137.7, 143.2, 143.5; MS *m/z* (FAB) 696 ([M + H]$^+$). Anal. Calcd for $C_{35}H_{41}N_3O_6S_3$: C, 60.4; H, 5.9; N, 6.0. Found: C, 60.9; H, 5.7; N, 6.2.

***N,N′,N″,N‴*-Tetratosyl-2,6,9,13-tetraaza[14]paracyclophane (12a):** 90% yield; mp 221–223 °C; ^{1}H NMR δ 1.47 (m, 6 H), 2.43 (s, 6 H), 2.46 (s, 6 H), 2.74 (s, 4 H), 2.96 (t, *J* = 7 Hz, 4 H), 3.08 (t, *J* = 7 Hz, 4 H), 4.14 (s, 4 H), 7.3–7.4 (m, 12 H), 7.6 (d, *J* = 8 Hz, 4 H), 7.7 (d, *J* = 8 Hz, 4 H); ^{13}C NMR δ 21.5, 29.1, 48.1, 48.2, 54.6, 127.2, 127.3, 129.8, 129.9, 134.9, 135.2, 136.7, 143.5, 143.6; MS *m/z* (FAB) 893 ([M + H]$^+$). Anal. Calcd for $C_{44}H_{52}N_4O_8S_4$: C, 59.1; H, 5.9; N, 6.2. Found: C, 59.3; H, 6.0; N, 6.2.

***N,N′,N″,N‴,N⁗*-Pentatosyl-2,5,8,11,14-pentaaza[15]paracyclophane (13a):** 86% yield; mp 125–131 °C; ^{1}H NMR δ 2.44 (m, 15 H), 2.8–3.1 (m, 16 H), 4.25 (s, 4 H), 7.19 (s, 4 H), 7.25–7.4 (m, 10 H), 7.5–7.8 (m, 10 H); ^{13}C NMR δ 22.1, 47.1, 50.2, 50.8, 52.1, 53.8, 127.9, 128.0, 129.8, 130.5, 134.0, 135.3, 135.7, 136.2, 144.3, 144.3, 144.7; MS *m/z* (FAB) 1062 ([M + H]$^+$). Anal. Calcd for $C_{51}H_{59}N_5O_{10}S_5$: C, 57.7; H, 5.6; N, 6.6. Found: C, 57.7; H, 5.8; N, 6.7.

13,14,16,17-Tetramethyl-*N,N′,N″*-tritosyl-2,6,10-triaza[11]paracyclophane (10b): 81% yield; mp 186–190 °C; ^{1}H NMR δ 1.12 (m, 4 H), 2.28 (s, 12 H), 2.40 (s, 3 H), 2.48 (s, 6 H), 2.60 (t, *J* = 7 Hz, 4 H), 2.76 (t, *J* = 8 Hz, 4 H), 4.43 (s, 4 H), 7.27 (d, *J* = 8 Hz, 2 H), 7.38 (d, *J* = 8 Hz, 4 H), 7.53 (d, *J* = 8 Hz, 2 H), 7.75 (d, *J* = 8 Hz, 4 H); ^{13}C NMR δ 16.9, 21.5, 21.6, 30.4, 45.7, 47.4, 48.4, 126.9, 127.4, 129.7, 129.9, 131.7, 134.4, 135.4, 135.6, 143.4, 143.6; MS *m/z* (FAB) 752 ([M + H]$^+$). Anal. Calcd for $C_{39}H_{49}N_3O_6S_3$: C, 62.3; H, 6.6; N, 5.6. Found: C, 62.0; H, 6.5; N, 5.6.

14,15,17,18-Tetramethyl-*N,N′,N″,N‴*-tetratosyl-2,5,8,11-tetraaza[12]paracyclophane (11b): 71% yield; mp 270–276 °C; ^{1}H NMR δ 2.16 (s, 12 H), 2.44 (s, 6 H), 2.47 (s, 6 H), 2.48 (s, 4 H), 2.78 (m, 8 H), 4.31 (s, 4 H), 7.31 (d, *J* = 8 Hz, 4 H), 7.39 (d, *J* = 8 Hz, 4 H), 7.70 (d, *J* = 8 Hz, 4 H), 7.81 (d, *J* = 8 Hz, 4 H); ^{13}C NMR δ 17.5, 22.1, 22.2, 45.6, 48.5, 48.9, 50.7, 127.9, 128.2, 130.4, 130.5, 131.7, 133.6, 135.9, 136.0, 144.2, 144.5; MS *m/z* (FAB) 921 ([M + H]$^+$). Anal. Calcd for $C_{46}H_{56}N_4O_8S_4$: C, 60.0; H, 6.1; N, 6.1. Found: C, 60.2; H, 6.0; N, 5.9.

16,17,19,20-Tetramethyl-*N,N′,N″,N‴*-tetratosyl-2,6,9,13-tetraaza[14]paracyclophane (12b): 76% yield; mp 161–163 °C; ^{1}H NMR δ 1.47 (m, 4 H), 2.35 (s, 12 H), 2.41 (s, 6 H), 2.48 (s, 6 H), 2.78 (s, 4 H), 2.95 (m, 8 H), 4.36 (m, 4 H), 7.26 (d, *J* = 8 Hz, 4 H), 7.42 (d, *J* = 8 Hz, 4 H), 7.53 (d, *J* = 8 Hz, 4 H), 7.78

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(d, J = 8 Hz, 4 H); ^{13}C NMR δ 16.8, 21.5, 21.6, 28.5, 46.0, 47.6, 47.9, 49.2, 127.1, 127.6, 129.8, 129.9, 131.3, 133.9, 135.5, 135.8, 143.4, 143.7; MS m/z (FAB) 949 ([M + H]$^+$). Anal. Calcd for $C_{48}H_{60}N_4O_8S_4$: C, 60.7; H, 6.4; N, 5.9. Found: C, 60.2; H, 6.3; N, 5.8.

6,13,14,16,17-Pentamethyl-2,10-ditosyl-2,6,10-triaza[11]paracyclophane (14b): 50% yield; mp 245–247 °C; ^{1}H NMR δ 1.08 (m, 4 H), 1.77 (t, J = 7 Hz, 4 H), 2.04 (s, 3 H), 2.27 (s, 12 H), 2.47 (s, 6 H), 2.63 (t, J = 8 Hz, 4 H), 4.42 (s, 4 H), 7.39 (d, J = 8 Hz, 4 H), 7.75 (d, J = 8 Hz, 4 H); ^{13}C NMR δ 16.9, 21.5, 26.5, 43.8, 45.9, 48.2, 51.5, 127.3, 129.7, 131.5, 134.5, 135.2, 143.4; MS m/z (FAB) 612 ([M + H]$^+$). Anal. Calcd for $C_{33}H_{45}N_3O_4S_2$: C, 64.8; H, 7.4; N, 6.9. Found: C, 64.5; H, 7.3; N, 7.2.

Detosylation Procedures. Method A. 2,5,8,11-Tetraaza[12]paracyclophane (17a). Tetratosylated macrocycle **11a** (1.0 g, 1.5 mmol) and phenol (5 g, 53 mmol) were suspended in HBr/AcOH (33%, 40 mL). The mixture was stirred at 90 °C for 18 h, and then the solution was vacuum evaporated. The residue was suspended in a mixture of CH_2Cl_2 (20 mL) and water, the aqueous layer was washed several times with additional portions of CH_2Cl_2 (30 mL), basified with NaOH, and vacuum evaporated. The dry residue was extracted several times with $CHCl_3$ to give an oily product, which was chromatographed on silica with MeOH/NH_3/THF as eluent to afford **17a** as a waxy solid (170 mg, 0.69 mmol, 53%): ^{1}H NMR δ 2.06 (s, 4 H), 2.46 (m, 4 H), 2.76 (m, 4 H), 3.72 (s, 4 H), 7.31 (s, 4 H); ^{13}C NMR δ 46.2, 49.1, 49.3, 53.7, 129.7, 141.1. For analytical purposes, the tetraperchlorate was prepared by the addition of concentrated $HClO_4$ to an ethanolic solution of **17a**. Anal. Calcd for $C_{14}H_{28}N_4O_{16}Cl_4$: C, 25.9; H, 4.3; H, 8.6. Found: C, 26.0; H, 4.3; N, 8.4.

Detosylation Procedures. Method B. 13,14,16,17-Tetramethyl-2,6,10-triaza[11]paracyclophane (16b). Tosylated macrocycle **10b** (4 g, 5.3 mmol), Na_2HPO_4 (10 g, 70 mmol), and 5% sodium amalgam (80 g) were suspended in a mixture of MeOH/THF (40 mL/150 mL) and refluxed for 48 h. Water was added dropwise (CAUTION) to the solution at 0 °C to destroy excess sodium. The resulting suspension was filtered, and the organic solvents were vacuum evaporated. The residue was exhaustively extracted with CH_2Cl_2. After vacuum evaporation of the organic solvent, the oily product was chromatographed on silica (MeOH/NH_3) to give pure **16b** (0.82 g, 2.9 mmol, 54%): ^{1}H NMR δ 1.39 (m, 4 H), 2.15 (t, 4 H), 2.33 (s, 4 H), 2.38 (t, 4 H), 3.98 (s, 4 H); ^{13}C NMR δ 17.3, 30.5, 41.4, 46.0, 46.5, 133.5, 136.8. Anal. Calcd for $C_{18}H_{34}N_3O_{12}Cl_3$: C, 36.6; H, 5.8; N, 7.1. Found: C, 37.0; H, 5.7; N, 7.2.

2,5,8-Triaza[9]paracyclophane (15a): method A, 35% yield; ^{1}H NMR δ 1.92 (t, J = 10 Hz, 4 H), 2.56 (t, J = 10 Hz, 4 H), 3.80 (s, 4 H), 7.38 (s, 4 H); ^{13}C NMR δ 45.6, 52.1, 54.0, 130.5, 141.0. Anal. Calcd for $C_{12}H_{22}N_3O_{12}Cl_3$: C, 28.5; H, 4.4; N, 8.3. Found: C, 28.3; H, 4.5; N, 8.4.

2,6,10-Triaza[11]paracyclophane (16a): method A, 43%; ^{1}H NMR δ 1.35 (m, 4 H), 2.14 (t, J = 7 Hz, 4 H), 2.45 (m, 4 H), 3.70 (s, 4 H), 7.28 (s, 4 H); ^{13}C NMR δ 29.9, 41.7, 43.3, 52.9, 129.2, 140.2. Anal. Calcd for $C_{14}H_{26}N_3O_{12}Cl_3$: C, 31.5; H, 4.9; N, 7.9. Found: C, 31.2; H, 5.1; N, 7.7.

2,6,9,13-Tetraaza[14]paracyclophane (18a): method A, 52% yield; ^{1}H NMR δ 1.31 (m, 4 H), 2.21 (t, J = 8 Hz, 4 H), 2.30 (s, 4 H), 2.37 (m, 4 H), 3.6 (s, 4 H), 7.0 (s, 4 H); ^{13}C NMR δ 28.8, 43.8, 46.3, 49.0, 52.7, 128.1, 138.7. Anal. Calcd for $C_{16}H_{32}N_4O_{16}Cl_4$: C, 28.4; H, 4.8; N, 8.3. Found: C, 28.1; H, 4.7; N, 8.1.

2,5,8,11,14-Pentaaza[15]paracyclophane (19a): method A, 49% yield; ^{1}H NMR δ 2.2–2.6 (m, 16 H), 3.66 (s, 4 H), 7.19 (s, 4 H); ^{13}C NMR δ 47.9, 49.3, 49.4, 49.8, 53.5, 126.8, 140.2. Anal. Calcd for $C_{16}H_{34}N_5O_{20}Cl_5$: C, 24.2; H, 4.3; N, 8.8. Found: C, 24.4; H, 4.2; N, 9.0.

14,15,17,18-Tetramethyl-2,5,8,11-tetraaza[12]paracyclophane (17b): method B, 40% yield; ^{1}H NMR δ 1.96 (s, 4 H), 2.32 (s, 12 H), 2.41 (m, 4 H), 2.59 (m, 4 H), 3.98 (s, 4 H); ^{13}C NMR δ 16.9, 44.9, 46.3, 48.1, 48.5, 132.9, 136.5. Anal. Calcd for $C_{18}H_{36}N_4O_{16}Cl_4$: C, 30.6; H, 5.1; N, 7.9. Found: C, 30.8; H, 5.0; N, 8.0.

16,17,19,20-Tetramethyl-2,6,9,13-tetraaza[14]paracyclophane (18b): method B, 51% yield; ^{1}H NMR δ 1.50 (m, 4 H), 2.34 (s, 12 H), 2.47 (s, 4 H), 2.50–2.55 (m, 8 H), 4.03 (s, 4 H); ^{13}C NMR δ 16.8, 29.5, 44.9, 47.1, 47.5, 49.6, 133.0, 135.8. Anal. Calcd for $C_{20}H_{40}N_4O_{16}Cl_4$: C, 32.8; H, 5.5; N, 7.6. Found: C, 32.5; H, 5.6; N, 7.8.

1,10-Dibenzyl-*N*,*N*′,*N*″,*N*‴-tetratosyl-1,4,7,10-tetraazadecane (3, R = Ts, R′ = Bn). Tosylated polyamine **3** (R = Ts, R′ = H) (0.55 g, 0.7 mmol), benzyl chloride (0.18 g, 1.4 mmol), and K_2CO_3 were suspended in CH_3CN (50 mL) and refluxed for 16 h. After filtration the solution was vacuum evaporated to give quantitatively the pure compound as a white solid (0.66 g, 0.7 mmol). Further purification could be accomplished by chromatography over silica (CH_2Cl_2): ^{1}H NMR δ 2.38 (s, 6 H), 2.41 (s, 6 H), 2.77 (m, 4 H), 2.95 (s, 4 H), 3.26 (m, 4 H), 7.27–7.40 (m, 18 H), 7.79 (d, 8 H); ^{13}C NMR δ 21.5, 48.3, 49.5, 53.8, 127.3, 127.9, 128.7, 128.9, 129.7, 129.9, 134.7, 135.8, 136.5, 143.5. Anal. Calcd for $C_{48}H_{54}N_4S_4O_8$: C, 61.1; H, 5.8; N, 5.9. Found: C, 61.4; H, 5.8; N, 6.0.

1,7-Dibenzyl-*N*,*N*′,*N*″-tritosyl-1,4,7-triazaheptadecane (1, R = Ts, R′ = Bn): ^{1}H NMR δ 2.38 (s, 3 H), 2.45 (s, 3 H), 2.71 (m, 4 H), 3.15 (m, 4 H), 4.20 (s, 4 H), 7.10 (s, 4 H), 7.33 (m, 16 H), 7.75 (d, 6 H); ^{13}C NMR δ 21.4, 21.5, 47.9, 49.0, 53.5, 126.9, 127.2, 127.9, 128.7, 128.8, 129.5, 129.8, 134.5, 135.9, 136.2, 143.3, 143.5. Anal. Calcd for $C_{39}H_{43}N_3S_3O_6$: C, 62.8; H, 5.8; N, 5.6. Found: C, 63.1; H, 5.8; N, 5.4.

1,9-Dibenzyl-*N*,*N*′,*N*″-tritosyl-1,5,9-triazanonadecane (2, R = Ts, R′ = Bn): ^{1}H NMR δ 1.39 (m, 4 H), 2.41 (s, 3 H), 2.45 (s, 6 H), 2.70 (t, 4 H), 2.98 (t, 4 H), 4.22 (s, 4 H), 7.22–7.34 (m, 16 H), 7.49 (d, 2 H), 7.70 (d, 4 H); ^{13}C NMR δ 21.5, 27.7, 46.1, 46.2, 52.7, 127.0, 127.2, 127.9, 128.4, 128.6, 129.6, 129.8, 136.1, 136.3, 143.2, 143.4. Anal. Calcd for $C_{41}H_{47}N_3S_3O_6$: C, 63.6; H, 6.1; N, 5.4. Found: C, 63.3; H, 6.0; N, 5.5.

1,12-Dibenzyl-*N*,*N*′,*N*″,*N*‴-tetratosyl-1,5,8,12-tetraazadodecane (4, R = Ts, R′ = Bn): ^{1}H NMR δ 1.62 (m, 4 H), 2.43 (s, 12 H), 2.87 (t, 4 H), 3.04 (s, 4 H), 3.10 (t, 4 H), 4.25 (s, 4 H), 7.2–7.4 (m, 18 H), 7.6 (d, 4 H), 7.7 (d, 4 H); ^{13}C NMR δ 21.5, 28.1, 45.9, 47.8, 48.6, 52.6, 127.2, 127.8, 129.8, 136.2, 143.4, 143.5. Anal. Calcd for $C_{50}H_{58}N_4S_4O_8$: C, 61.8; H, 6.0; N, 5.8. Found: C, 61.5; H, 6.1; N, 5.8.

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