A New Synthetic Method for $(Aza)_n[3^n]$cyclophanes by Diethyl Phosphoramidates

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Abstract: $(Aza)_n[3^n]$cyclophanes are synthesized by the N-alkylation of diethyl phosphoramidates with bis(bromomethyl)arenes under phase-transfer conditions or anhydrous conditions in the presence of an appropriate base. The method affords *N*-(diethoxyphosphoryl)$(aza)_n[3^n]$cyclophanes in moderate yields and can be applied to the synthesis of various types of azacyclophanes. The N-phosphorylated cyclophanes are highly soluble in organic solvents and the diethoxyphosphoryl groups are readily cleaved under acidic conditions to give the corresponding secondary amines.

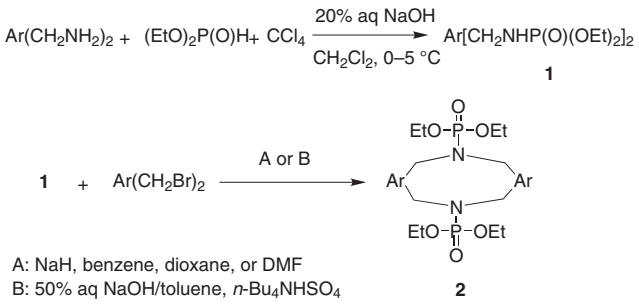
Key words: cyclophanes, phosphorylations, amines, host–guest systems, macrocycles

In host–guest chemistry, hydrophobic interaction plays an important role for the inclusion of guest molecules into the cavity of host molecules. Hydrophobic interaction becomes much more important in polar solvents than in nonpolar solvent, especially it is most effective in aqueous media. Therefore many water-soluble host molecules are designed and used for the study of host–guest interactions and construction of artificial enzyme system.[1] In this respect, azacyclophanes are convenient molecules for introducing functional groups on N atoms and making them soluble in water. During the course of our azacyclophane studies, convenient and widely applicable synthetic methods have been explored and developed.[2] There are several established synthetic methods, but each has own availabilities and drawbacks. Thus, development of new and various types of synthetic methods is favorable because the best method should be chosen for the synthesis of target molecule.

We wish to describe here a new synthetic method of $(aza)_n[3^n]$cyclophanes by N-alkylation reaction of *N,N′*-dialkylphosphoramidates **1** with bis(bromomethyl) compounds in the presence of base such as aqueous NaOH under phase-transfer conditions or NaH under anhydrous conditions.

Zwierzak et al. reported that diethyl *N*-alkyl- or *N*-arylphosphoramidates can be readily alkylated with primary alkyl halides[3] and afford respective secondary amines. Removal of diethoxyphosphoryl group proceeded smoothly at room temperature with gaseous HCl in THF or benzene and gave corresponding amine hydrochlorides. A related application for the synthesis of macrocyclic compounds was reported.[4] We thus applied this method for the synthesis of $(aza)_n[3^n]$cyclophanes.

The *N,N′*-bis[(diethoxyphosphoryl)aminomethyl]arenes **3**–**7** (general structure ≡ **1**) were prepared by treatment of corresponding amines with phosphonic acid diethyl ester and CCl_4 (Scheme 1) in CH_2Cl_2 under phase-transfer conditions (triethylbenzylammonium chloride, 20% aq NaOH) at low temperatures (0–5 °C). The resultant phosphoramidate derivatives were purified by silica gel chromatography with CH_2Cl_2 as an eluent and gave essentially pure phosphoramidates in modest to good yields (Table 1). The phosphoramidates are highly soluble in common organic solvents and they are generally colorless oils or low-melting crystals.



Scheme 1 Preparation of *N,N′*-bis[(diethoxyphosphoryl)aminomethyl]arenes and coupling with bis(bromomethyl)arenes

The resultant diethyl phosphoramidates were coupled with corresponding bis(bromomethyl) compounds under phase-transfer conditions (50% aq NaOH/toluene, Bu_4NX) or anhydrous conditions such as NaH/benzene, NaH/dioxane, or NaH/DMF. Besides the diaza[3.3]cyclophanes, its tetramers and hexamers were obtained except in the paracyclophane case, in which diaza[3.3]paracyclophane was not formed (Scheme 2). The use of Cs_2CO_3 as a base did not give cyclic products. For example, a reaction between 1,4-bis(bromomethyl)benzene and the amidate **3** in DMF in the presence of Cs_2CO_3 at 60 °C for 16 hours did not give macrocyclic compounds **8** or **9** but a mixture of acyclic compounds was obtained.

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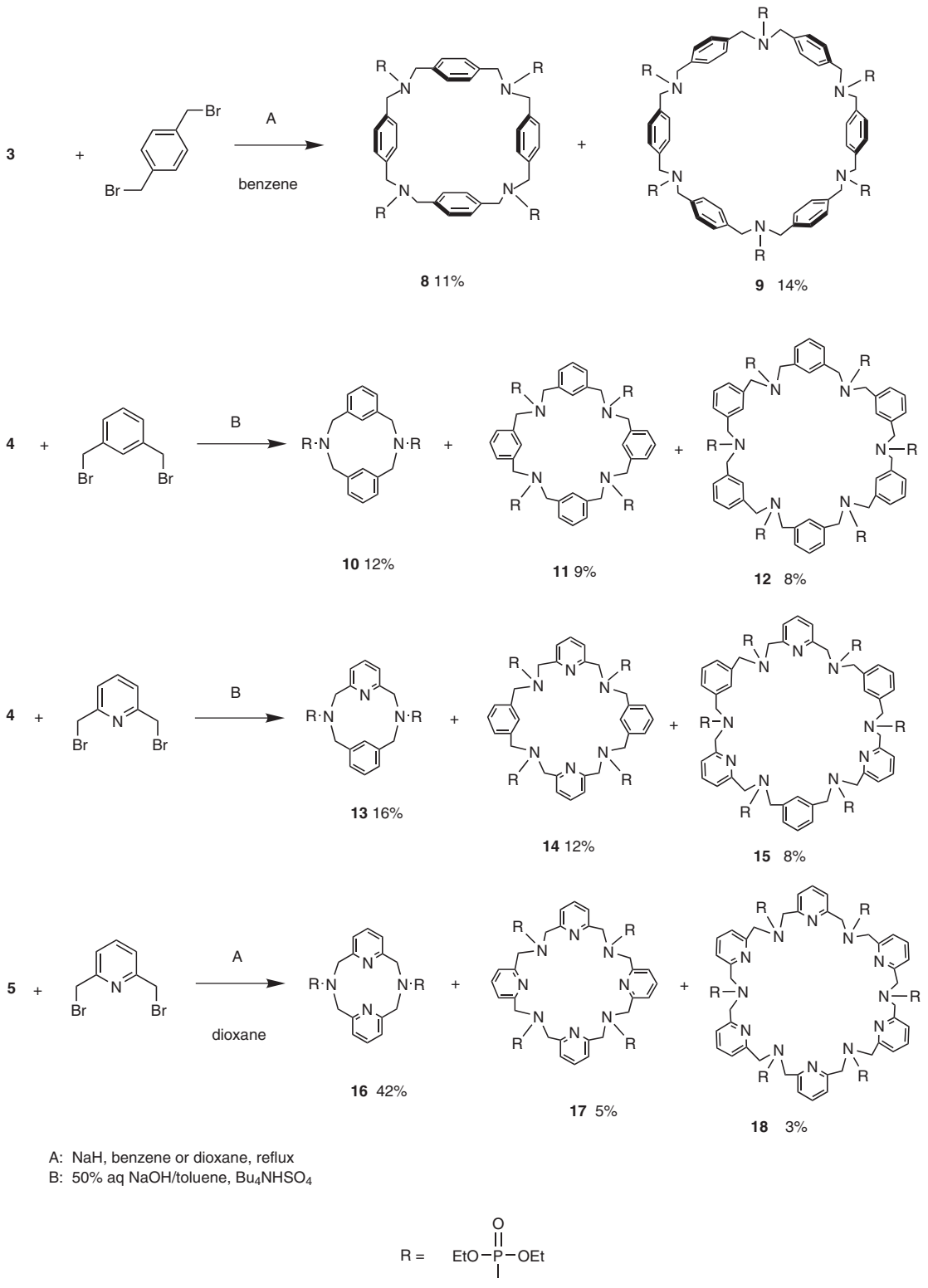
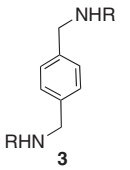
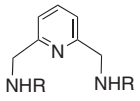
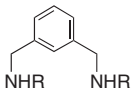
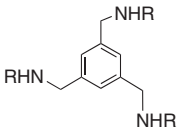
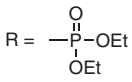
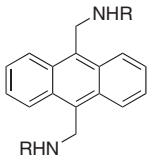
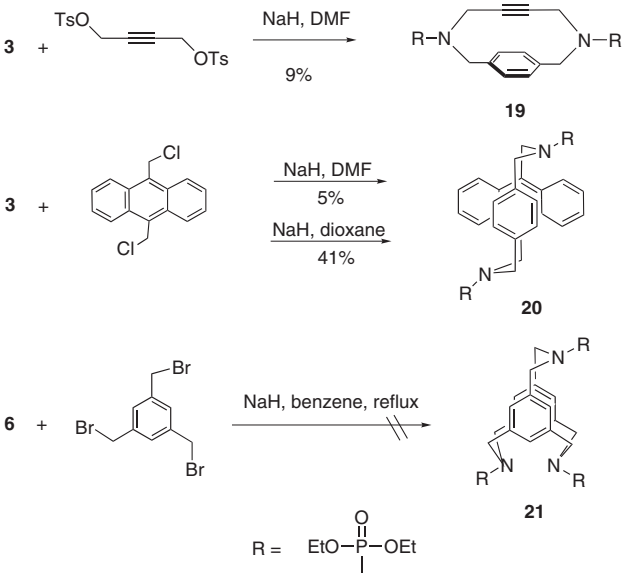


Scheme 2 Synthesis of $[(EtO)_2PO]_n(aza)_n[3^n]$cyclophanes

As shown in Scheme 3, alkylation of the amidate **3** by but-2-yne-1,4-diol ditosylate (NaH, DMF) provided [8]paracyclophane-4-yne **19** in 9% yield. Furthermore, diaza[3.3]paracyclo(9,10)anthracenophane derivative **20** was prepared by the reaction of the amidate **3** and 9,10-bis(chloromethyl)anthracene under NaH/DMF or NaH-dioxane conditions, in which the latter gave better yield (41%) than the former (5%). Related diaza[3.3]paracyclo(9,10)anthracenophane derivative was reported by Okamoto et al.[5]

Table 1 *N,N′*-Bis[(diethoxyphosphoryl)aminomethyl]arenes Prepared

Product	Yield (%)	Product	Yield (%)
 **3**	72	 **5**	31
 **4**	89	 **6**	52
		 **7**	54



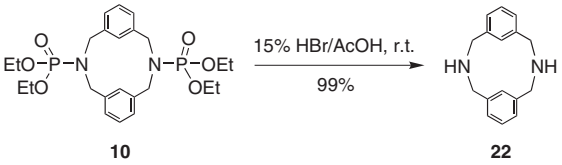
Scheme 3 Synthesis of $[(EtO)_2PO]_n(aza)_n[3^n]$cyclophanes

However, triply-bridged cyclophane, triaza[3_3](1,3,5)cyclophane **21** was not obtained, but the reason is not clear so far. Similarly, the reaction between the amidate **7** and 9,10-bis(chloromethyl)anthracene did not afford the expected $(aza)_n[3^n]$(9,10)anthracenophane.

A special feature of this method is that one can obtain higher cyclic oligomers which are difficult to prepare by other cyclization methods. For example, hexaaza derivatives, **9**,**12**,**15**, and **18**, which are the potential ligands of polynuclear metal complexes, were obtained.

Different from commonly used *N*-tosyl-protected cyclophanes, cyclic phosphoramidate derivatives are very soluble materials, and therefore, further treatments are convenient. Actually, *N*-Ts-$(aza)_n[3^n]$paracyclophanes are difficult to separate each other because of their low solubility.[2a] Furthermore, cleavage of Ts group of *N*-Ts-azacyclophanes or macrocyclic compounds are sometimes a problem. Several cleavage conditions were developed in order to overcome this problem and it is necessary to choose better method of deprotection.[6] In this respect, recently developed azacyclophane synthetic methods which employ CF_3CONH_2,[2b] NH_2CN,[2c] Ns (*o*,*p*-nitrobenzenesulfonamide),[7] and SES (β-trimethylsilylethanesulfonamides)[8] should be considered, as well as this phosphoramidate method according to the properties of target cyclophanes and their starting materials.

The N-protected diethoxyphosphoryl group was readily removed by treatment with 15% HBr in AcOH (commercially available) at room temperature. After the usual work-up, secondary amine **22** was obtained in 99% yield (Scheme 4).



Scheme 4 Cleavage of phosphoryl group

In summary, the advantages of this method are as follows:

(1) Starting material, phosphonic acid diethyl ester is inexpensive, and N-phosphorylation of the corresponding amine proceeds smoothly.

(2) The resultant N-phosphorylated cyclophanes are highly soluble in common organic solvents and easy to handle and separate.

(3) Although the yields of N-phosphorylated cyclophanes are modest, this method can be applied for the synthesis of various azacyclophanes including pyridinophanes, a cyclophane containing an acetylenic unit, and anthracenophane. Especially, higher oligomers, which are not obtained by toluenesulfonamide method, are obtained.

(4) The protecting groups are readily removed.

All melting points were measured on Yanaco MP-S3 apparatus, and are uncorrected. The ^{1}H NMR spectra were recorded on JEOL JNM-GX 270 (270MHz) spectrometer. Chemical shifts are reported as δ values (ppm) relative to the internal tetramethylsilane. Mass spectra were measured on JEOL JMS-HX110A spectrometer. Elemental analyses were performed by the Service Centre of the Elementary Analysis of Organic Compounds affiliated to the Faculty of Science, Kyushu University.

Silica gel chromatography was performed on Merck silica gel 60 (43–60 mμ), Fuji Silysia BW-300 and BW-350 (NH type), Merck silica gel PF_{254} for preparative TLC, and Merck silica gel F_{254} (0.2 mm on glass) for analytical purpose. Sephadex LH-20 and EtOH were used for gel filtration chromatography. For the separation of oligomers which are difficult to separate by the silica gel or Sephadex chromatography, recycle preparative HPLC on GPC (JAIGEL-

1H and 2H) with $CHCl_3$ as eluent was used (LC-908, Japan Analytical Industry Co., Ltd.).

Phosphonic acid diethyl ester, and 1,3- and 1,4-bis(aminomethyl)benzenes and were purchased from Tokyo Kasei Co. Ltd. Benzene, dioxane, and DMF were dried over molecular sieves 4Å. 9,10-Bis(aminomethyl)anthracene was prepared according to the literature method.[9]

N,N′-1,4-Bis[(diethoxyphosphoryl)aminomethyl]benzene (3); Typical Procedure

To a stirred mixture of NaOH (12.0 g, 25 mmol) in H_2O (60 mL), $BnEt_3NCl$ (1.50 g, 8.1 mmol), CCl_4 (40 mL, 414 mmol) and CH_2Cl_2 (100 mL), was added dropwise a CH_2Cl_2 solution (100 mL) of 1,4-bis(aminomethyl)benzene (6.81 g, 50.0 mmol) and a CH_2Cl_2 solution (100 mL) of phosphonic acid diethyl ester (18.0 g, 130 mmol) simultaneously over a period of 1 h at 0–5 °C. After addition, the mixture was stirred at 0–5 °C for 10 h and then at r.t. for 3 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated to dryness. The residue was purified by silica gel chromatography with CH_2Cl_2 to give **3** (14.7 g, 72%); colorless crystals (CH_2Cl_2–hexane); mp 93.0–94.3 °C.

^{1}H NMR: δ = 1.30 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 3.11–3.14 (m, 2 H, NH), 3.97–4.13 (m, 12 H, CH_2N and OCH_2CH_3), 7.30 (s, 4 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{16}H_{31}N_2O_6P_2$: 409.1657; found: 409.1636 (100).

N,N′-1,3-Bis[(diethoxyphosphoryl)aminomethyl]benzene (4)

Colorless oil (89%).

^{1}H NMR: δ = 1.29 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 3.52–3.54 (m, 2 H, NH), 3.95–4.11 (m, 12 H, CH_2N and OCH_2CH_3), 7.24–7.29 (m, 3 H, ArH), 7.33 (s, 1 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{16}H_{31}N_2O_6P_2$: 409.1657; found: 409.1667 (100).

N,N′-2,6-Bis[(diethoxyphosphoryl)aminomethyl]pyridine (5)

Colorless oil (31%).

^{1}H NMR: δ = 1.21 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 3.89–4.04 (m, 8 H, OCH_2CH_3), 4.13 (d, *J* = 14 Hz, 4 H, CH_2N), 7.16 (d, *J* = 7 Hz, 2 H, ArH), 7.57 (t, *J* = 7 Hz, 1 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{15}H_{30}N_3O_6P_2$: 410.1610; found: 410.1623 (100).

N,N′,N″-1,3,5-Tris[(diethoxyphosphoryl)aminomethyl]benzene (6)

Colorless oil (52%).

^{1}H NMR: δ = 1.29 (t, *J* = 7 Hz, 18 H, OCH_2CH_3), 3.46–3.50 (m, 3 H, NH), 3.97–4.17 (m, 18 H, CH_2N and OCH_2CH_3), 7.33 (s, 3 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{21}H_{43}N_3O_9P_3$: 574.2212; found: 574.2186 (100).

N,N′-9,10-Bis[(diethoxyphosphoryl)aminomethyl]anthracene (7)

Colorless crystals (54%); mp 214.5–216 °C (CH_2Cl_2–hexane).

^{1}H NMR: δ = 1.32 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 2.82–2.95 (m, 2 H, NH), 3.99–4.16 (m, 8 H, OCH_2CH_3), 5.09 (t, *J* = 6 Hz, 4 H, CH_2N), 7.57–7.60 (m, 4 H, ArH), 8.39–8.45 (m, 4 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{24}H_{35}N_2O_6P_2$: 509.1970; found: 509.1993 (100).

N,N′,N″,N‴-Tetrakis(diethoxyphosphoryl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (8) and *N,N′,N″,N‴,N⁗,N⁗′*-Hexakis(diethoxyphosphoryl)-2,11,20,29,38,47-hexaaza[3.3.3.3.3.3]paracyclophane (9); Typical Procedure

Method A (in benzene): To a stirred mixture of benzene (150 mL) and NaH (60%, 1.10 g), was added dropwise a solution of the amidate **3** (4.90 g, 10.2 mmol) in benzene (200 mL) and a solution of 1,4-bis(bromomethyl)benzene (3.30 g, 12.5 mmol) in benzene (200 mL) simultaneously over a period of 1 h at r.t. After the addition, the mixture was refluxed overnight. After cooling, H_2O (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was separated by Sephadex (LH-20) chromatography with EtOH to give the crude product (3.50 g). A sample (100 mg) was subjected to preparative recycle HPLC (GPC, $CHCl_3$) to afford pure tetraaza[3^4]paracyclophane derivative **8** (17 mg, 11%) and hexaaza[3^6]paracyclophane derivative **9** (21mg, 14%).

8

Colorless oil.

^{1}H NMR: δ = 1.36 (t, *J* = 7 Hz, 24 H, OCH_2CH_3), 3.99–4.17 (m, 32 H, CH_2N and OCH_2CH_3), 6.94 (s, 16 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{48}H_{73}N_4O_{12}P_4$: 1021.4175; found: 1021.4164 (100).

9

Colorless oil.

^{1}H NMR: δ = 1.35 (t, *J* = 7 Hz, 36 H, OCH_2CH_3), 4.03–4.15 (m, 48 H, CH_2N and OCH_2CH_3), 7.27 (s, 24 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{72}H_{109}N_6O_{18}P_6$: 1531.6224; found: 1531.6233 (100).

N,N′-Bis(diethoxyphosphoryl)-2,11-diaza[3.3]metacyclophane (10), *N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-2,11,20,29-tetraaza[3.3.3.3]metacyclophane (11), and *N,N′,N″,N‴,N⁗,N⁗′*-Hexakis(diethoxyphosphoryl)-2,11,20,29,38,47-hexaaza[3.3.3.3.3.3]metacyclophane (12); Typical Procedure

Method B: To a stirred mixture of aq NaOH (15 g in 15 mL of H_2O), Bu_4NHSO_4 (300 mg), and toluene (100 mL), was added dropwise a toluene solution (50 mL) of the amidate **4** (4.08 g, 10.0 mmol) and a toluene solution (50 mL) of 1,3-bis(bromomethyl)benzene (3.43 g, 13.0 mmol) simultaneously over a period of 1 h at reflux temperature. After addition, the mixture was refluxed for 11 h. After cooling, H_2O (50 mL) was added and the organic layer was separated, washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to dryness in vacuo to give dark yellow oil. The oil was subjected to Sephadex (LH-20) chromatography with EtOH as an eluent. The first fraction (1.76 g) contained [3^4]metacyclophane and its higher oligomers, whereas the second fraction (0.93 g) contained mainly [3^2]metacyclophane. Further separation of a sample (100 mg) of the first fraction by recycle HPLC (GPC, $CHCl_3$) afforded tetraaza[3^4]- and hexaaza[3^6]metacyclophanes **11** (18 mg, 6%) and **12** (18 mg, 6%). Separation of the second fraction (100 mg) provided diaza[3^2]- **10** (60 mg, 11%) and tetraaza[3^4]azacyclophane **11** (9 mg, 2%, total 8%).

10

Colorless oil.

^{1}H NMR: δ = 1.41 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 4.15–4.23 (m, 16 H, CH_2N and OCH_2CH_3), 6.91–6.93 (m, 8 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{24}H_{37}N_2O_6P_2$: 511.2127; found: 511.2151 (100).

11
Colorless oil.

^{1}H NMR: δ = 1.32 (t, *J* = 7 Hz, 24 H, OCH_2CH_3), 3.97–4.18 (m, 32 H, CH_2N and OCH_2CH_3), 7.27–7.33 (m, 16 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{48}H_{73}N_4O_{12}P_4$: 1021.4175; found: 1021.4129 (100).

12
Colorless oil.

^{1}H NMR: δ = 1.29 (t, *J* = 7 Hz, 36 H, OCH_2CH_3), 3.98–4.15 (m, 48 H, CH_2N and OCH_2CH_3), 7.16–7.23 (m, 24 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{72}H_{109}N_6O_{18}P_6$: 1531.6224; found: 1531.6202 (100).

***N,N′*-Bis(diethoxyphosphoryl)-2,11-diaza[3.3]metacyclo(2,6)pyridinophane (13), *N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-2,11,20,29-tetraaza[3.3.3.3]metacyclo(2,6)pyridinophane (14), and *N,N′,N″,N‴,N⁗,N⁗′*-Hexakis(diethoxyphosphoryl)-2,11,20,29,38,47-hexaaza[3.3.3.3.3.3]metacyclo(2,6)pyridinophane (15)**
Method B: A crude product obtained from the amidate **4** (4.08 g, 10.0 mmol) and 2,6-bis(bromomethyl)pyridine (3.45 g, 13.0 mmol) was subjected to Sephadex (LH-20) chromatography (EtOH). The first fraction (0.88 g) contained [3^6]cyclophane and its higher oligomers, and the second fraction (1.69 g) contained lower oligomers. Each sample (150 mg) of the fraction was further separated by recycle HPLC (GPC, $CHCl_3$) to afford **13**, **14**, and **15**.

13
Colorless oil (72 mg, 16%).

^{1}H NMR: δ = 1.41 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 4.14–4.45 (m, 16 H, CH_2N and OCH_2CH_3), 6.89–7.51 (m, 6 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{23}H_{36}N_3O_6P_2$: 512.2079; found: 512.2016 (100).

14
Colorless oil (53 mg, 12%).

^{1}H NMR: δ = 1.24 (t, *J* = 7 Hz, 24 H, OCH_2CH_3), 4.02–4.15 (m, 32 H, CH_2N and OCH_2CH_3), 7.15–7.28 (m, 12 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{46}H_{71}N_6O_{12}P_4$: 1023.4081; found: 1023.4128 (100).

15
Colorless oil (57 mg, 8%).

^{1}H NMR: δ = 1.29 (t, *J* = 7 Hz, 36 H, OCH_2CH_3), 3.98–4.15 (m, 48 H, CH_2N and OCH_2CH_3), 7.16–7.23 (m, 18 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{69}H_{106}N_9O_{18}P_6$: 1534.6082; found: 1534.6206 (100).

***N,N′*-Bis(diethoxyphosphoryl)-2,11-diaza[3.3](2,6)pyridinophane (16), *N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-2,11,20,29-tetraaza[3.3.3.3](2,6)pyridinophane (17), and *N,N′,N″,N‴,N⁗,N⁗′*-Hexakis(diethoxyphosphoryl)-2,11,20,29,38,47-hexaaza[3.3.3.3.3.3](2,6)pyridinophane (18)**
Method A (in dioxane): A reaction mixture obtained from the amidate **5** (2.05 g, 5.00 mmol) and 2,6-bis(bromomethyl)pyridine (1.35 g, 5.10 mmol) was treated as described above and the resultant mixture was separated by silica gel column chromatography with CH_2Cl_2–EtOAc (1:1), followed by preparative silica gel TLC (CH_2Cl_2–EtOAc, 1:1) to afford **16** (1.08 g, 42%), **17** (128 mg, 5%), and **18** (77 mg, 3%).

16
Colorless oil.

^{1}H NMR: δ = 1.43 (t, *J* = 7 Hz, 12 H, OCH_2CH_3), 4.16–4.24 (m, 8 H, OCH_2CH_3), 4.47 (d, *J* = 16 Hz, 8 H, CH_2N), 6.98 (d, *J* = 7 Hz, 4 H, ArH), 7.25(t, *J* = 7 Hz, 2 H, ArH).

HRMS (FAB, M+H$^+$): *m*/*z* calcd for $C_{22}H_{35}N_4O_6P_2$: 513.2032; found: 513.2039 (100).

17
Colorless oil.

^{1}H NMR: δ = 1.26 (t, *J* = 7 Hz, 24 H, OCH_2CH_3), 3.99–4.14 (m, 16 H, OCH_2CH_3), 4.27 (d, *J* = 14 Hz, 16 H, CH_2N), 7.29 (d, *J* = 10 Hz, 8 H, ArH), 7.58 (t, *J* = 10 Hz, 4 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{44}H_{69}N_8O_{12}P_4$: 1025.3985; found: 1025.4000 (100).

18
Colorless oil.

^{1}H NMR: δ = 1.22 (t, *J* = 7 Hz, 36 H, OCH_2CH_3), 4.01–4.08 (m, 24 H, OCH_2CH_3), 4.23 (d, *J* = 14 Hz, 24 H, CH_2N), 7.22 (d, *J* = 10 Hz, 12 H, ArH), 7.55(t, *J* = 10 Hz, 6 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{66}H_{103}N_{12}O_{18}P_6$: 1537.5939; found: 1537.5991 (100).

***N,N′*-Bis(diethoxyphosphoryl)-2,7-diaza[8]paracyclophane-4-yne (19)**
Method A (in DMF): A reaction mixture obtained from the amidate **3** (2.04 g, 5.00 mmol) and 2-butyne-1,4-diol ditosylate (2.56 g, 6.49 mmol) was treated as described above to give the crude product (1.35 g). The crude product was subjected to silica gel column chromatography with EtOAc to afford **19** as a colorless oil (206 mg, 9%).

^{1}H NMR: δ = 1.28–1.35 (m, 12 H, OCH_2CH_3), 4.01–4.16 (m, 12 H, CH_2N and OCH_2CH_3), 4.52 (d, *J* = 16 Hz, 4 H, CH_2N), 7.25–7.30 (m, 4 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{20}H_{32}N_2O_6P_2$: 459.1814; found: 459.1782 (100).

***N,N′*-Bis(diethoxyphosphoryl)-2,11-diaza[3.3]paracyclo(9,10)anthracenophane (20)**
Method A (in dioxane): A reaction mixture obtained from the amidate **3** (960 mg, 2.00 mmol) and 9,10-bis(chloromethyl)anthracene (720 mg, 2.60 mmol) was treated as described above to give the crude product, which was subjected to silica gel column chromatography with $CHCl_3$–EtOAc (1:1) as eluent to afford **21** (506 mg, 41%) as colorless crystals; mp 185.5–187 °C (CH_2Cl_2–hexane).

^{1}H NMR: δ = 1.45 (q, *J* = 7 Hz, 12 H, OCH_2CH_3), 4.00 (d, *J* = 6 Hz, 4 H, CH_2N), 4.21–4.37 (m, 8 H, OCH_2CH_3), 5.41 (d, *J* = 4 Hz, 4 H, CH_2N), 5.98 (s, 4 H, ArH), 7.55 (m, 4 H, ArH), 8.57 (m, 4 H, ArH).

HRMS (FAB, M + H$^+$): *m*/*z* calcd for $C_{32}H_{41}N_2O_6P_2$: 611.2440; found: 611.2345 (100).

2,11-Diaza[3.3]metacyclophane (22)
Compound **10** (102 mg, 0.200 mmol) was added to 15% HBr/AcOH (10 mL) and the mixture was stirred for 2 h at r.t. The resultant solution was poured into H_2O (100 mL) and made alkaline with aq NaOH. The solution was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were combined and dried ($MgSO_4$). Removal of the solvent yielded a colorless powder which was almost pure **22** (47 mg, 99%). All the spectral data were identical with an authentic sample of the 2,11-diaza[3.3]metacyclophane.

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