Synthesis and structural analysis of 2,11-diaza[3.3](3,5)pyridinophane †

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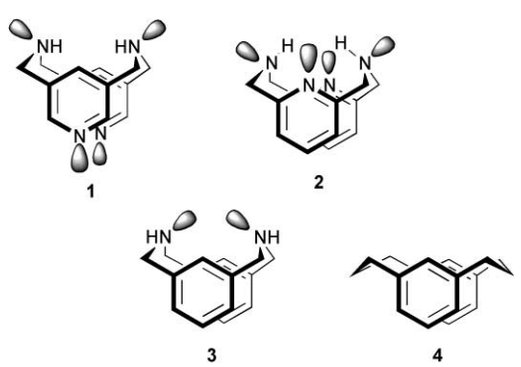
A possible bidentate receptor with two kinds of nitrogen atoms, 2,11-diaza[3.3](3,5)pyridinophane **1**, was synthesized. A VT ^{1}H NMR study and *ab initio* MO calculations indicated that the two conformers of **1**, boat–boat and chair–boat, have almost the same stabilities. The free energy barrier $\Delta G^{\ddagger}$ for the conformational change is estimated to be 10.4 kcal mol^{-1} ($T_c = -55$ °C). An X-ray crystallographic study revealed that **1** forms a hydrogen-bonding network in the crystalline state.

Introduction

Recently, we reported the synthesis and conformational studies of 2,11-diaza[3.3](2,6)pyridinophane **2** and 2,11-diaza[3.3]-metacyclophane **3**, where the flipping of the –CH_2NCH_2– bridges was studied by variable temperature (VT) NMR spectroscopy and theoretical calculations.[1]



A wide variety of pyridinophanes have been investigated so far. In particular, 2,6- and 2,5-disubstituted pyridine derivatives have been used predominantly with the aim of controlling the orientation of the lone pair electrons. In fact, pyridinophanes and macrocycles containing 2,6-disubstituted pyridine rings have been used as ligands for transition metal complexes[2] and as host molecules for the inclusion of metal cations[3] and organic molecules.[4] In contrast, studies concerning cyclophanes that incorporate 3,5-disubstituted pyridines are scarce and most of the cyclophanes investigated were thiacyclophanes.[5] A reason for the lack of studies may be the low stability of 2,6-unsubstituted 3,5-bis(halomethyl)pyridines, which are common precursors.

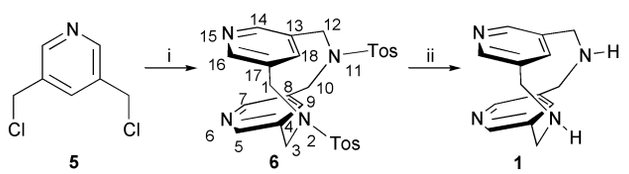
In this paper, we describe the first synthesis of 3,5-disubstituted diaza[3.3]pyridinophane **1**, its conformational analysis, and an X-ray crystallographic study.

† Electronic supplementary information (ESI) available: 3D coordinates for compounds **1** and **6** and for the three calculated conformers of compound **1** (**1BB**, **1CB** and **1CC**). See http://www.rsc.org/suppdata/p2/b2/b200402j/

Results and discussion

Synthesis

The title compound, 2,11-diaza[3.3](3,5)pyridinophane **1**, was synthesized in three steps from commercially available 3,5-lutidine in a 6% total yield (Scheme 1). Chlorination of



Scheme 1 *Reagents and conditions*: i, $TsNH_2$, NaH, DMF, 23%; ii, H_2SO_4, 87%.

3,5-lutidine with *N*-chlorosuccinimide in CCl_4 afforded 3,5-bis(chloromethyl)pyridine **5** (32%).[6] The coupling reaction of **5** with toluene-*p*-sulfonamide in the presence of NaH in DMF[7,8] afforded the dimer, *N*,*N*′-ditosyl-2,11-diaza[3.3](3,5)-pyridinophane **6** (23%). Detosylation of **6** was accomplished with conc. H_2SO_4 to give the desired product, **1** (87%).

Conformational analysis

[3.3]Pyridinophanes are expected to have three stable conformers in solution with *syn*-geometry, *i.e*. *syn*(boat–boat) BB, *syn*(chair–boat) CB, and *syn*(chair–chair) CC, as illustrated in Scheme 2, which arise from the flipping of the –CH_2NCH_2– bridges between the boat and the chair forms. A conformational study of [3.3]metacyclophane **4** in solution revealed that CC, which has the minimum steric hindrance, is the major conformer, and the free energy barrier $\Delta G^{\ddagger}$ for the flipping of the bridges is 11.6 kcal mol^{-1} ($T_c = -26$ °C).[9,10] In contrast, in the case of 2,11-diaza[3.3](2,6)pyridinophane **2**[1] the most stable conformer is BB because the attractive interaction between the lone pair electrons of the pyridine nitrogens and the amino proton of the bridges decreases the energy of BB. For 2,11-diaza[3.3]metacyclophane **3**,[1] the free energy difference between the conformers becomes small. The population of the conformers at −71 °C is BB : CB = 3.8 : 1.0, and, therefore, the free energy difference between BB and CB is only 0.5 kcal mol^{-1} at this temperature.

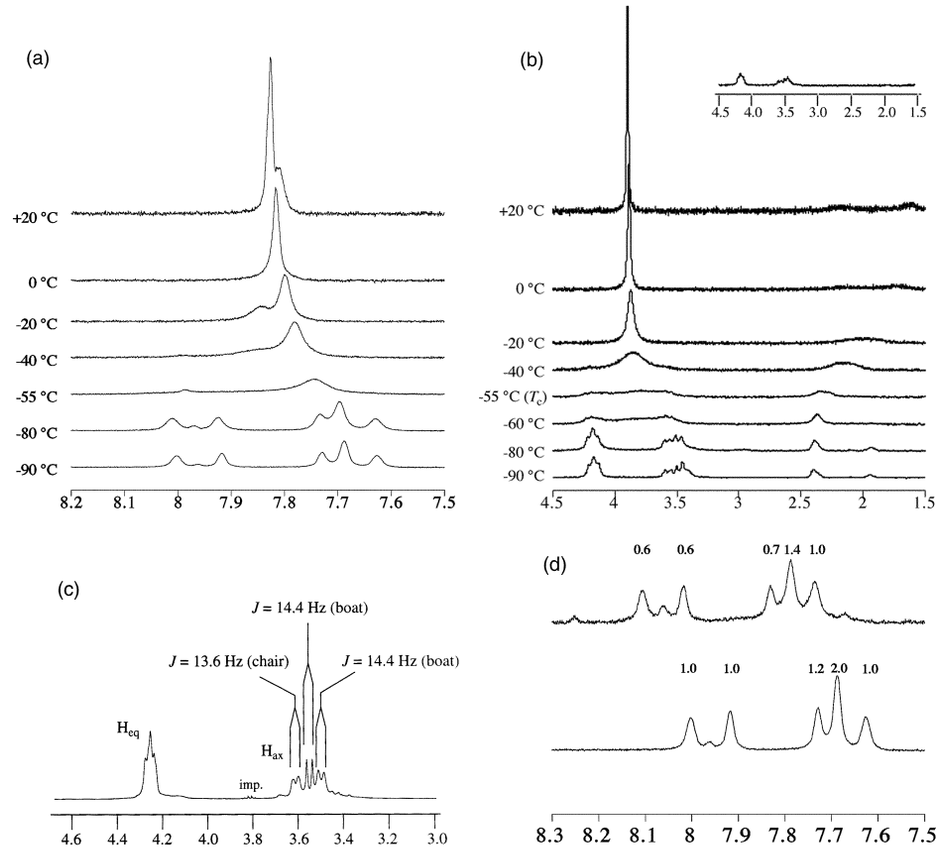
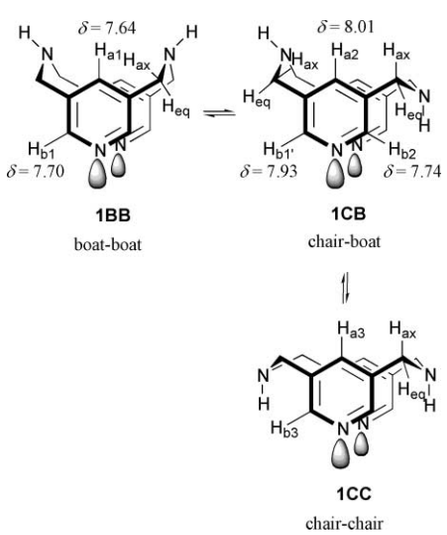


Fig. 1 (a) VT ^{1}H NMR spectra of the aromatic proton signals of **1** in CD_2Cl_2 (300 MHz). (b) VT ^{1}H NMR spectra of the benzylic and amino proton signals of **1** in CD_2Cl_2 (300 MHz). The inset is the spectrum at −90 °C after the addition of D_2O. (c) Expanded ^{1}H NMR spectrum (600 MHz) of the benzylic protons of **1** at −90 °C in CD_2Cl_2. (d) ^{1}H NMR spectra of the aromatic proton signals of **1** at −90 °C in CD_2Cl_2 (300 MHz). The numbers indicate the integrations of peaks. Top: after deuteration, bottom: before deuteration.



Scheme 2 The conformational equilibrium among the BB, CB, and CC conformers of 2,11-diaza[3.3](3,5)pyridinophane **1** *via* chair–boat flipping of the $-CH_2NCH_2-$ bridges. Assignments and ^{1}H chemical shifts of the aromatic proton signals are also shown.

VT ^{1}H NMR study in solution

The dynamic nature of azapyridinophane **1** was investigated by means of the VT NMR technique. Figs. 1a and 1b show the amino, benzylic and aromatic proton signals of the ^{1}H NMR spectra (300 MHz) at low temperatures in CD_2Cl_2. The sharp singlets of the benzylic (δ = 3.90) and aromatic proton signals (δ = 7.83, 7.81) at room temperature suggest rapid conformational interconversion of the bridges on the NMR time-scale. As the temperature is lowered, the benzylic proton signal begins to broaden, and resolves into two broad signals. Observation at 600 MHz shows that the higher field signal splits into three doublets (Fig. 1c), whereas, the lower field signal remains incompletely resolved. The amino proton signals appear as broad singlets (δ = 2.40, 1.94) at −90 °C. As indicated in the inset of Fig. 1b, the signals disappeared when a small amount of D_2O was introduced. The aromatic proton signals also broaden, and, eventually, are resolved into five singlets. The three axial benzylic proton signals and the integrals of the five aromatic proton signals (1 : 1 : 1 : 2 : 1) suggest that two kind of conformers exist at −90 °C.

A detailed conformational study of the [3.3]metacyclophane derivative[9b] established that the magnitude of the geminal coupling constant J_{gem} of the benzylic protons depends on the conformation of the trimethylene bridges (chair or boat); the J_{gem} values are 14.6 and 13.8 Hz for the boat and chair conformations, respectively. On the basis of these results, the benzylic protons of **1** at −90 °C can be assigned as follows: δ 3.63 (J = 13.6 Hz, H_{ax}, CB, chair), 3.57 (J = 14.4 Hz, H_{ax}, boat), and 3.52 (J = 14.4 Hz, H_{ax}, boat).

In order to assign the aromatic proton signals, partially deuterated **1** was prepared according to the literature procedure.[11] As a result of hydrogen–deuterium exchange in the pyridine moiety, the ratio of the integrals of H_a : H_b changed from 1.0 : 2.0 to 1.0 : 1.1 at rt in $CDCl_3$. The integrals of the five aromatic proton signals at −90 °C changed from 1.0 : 1.0 : 1.2 : 2.0 : 1.0 to 0.6 : 0.6 : 0.7 : 1.4 : 1.0 on deuteration (Fig. 1d). Therefore, δ = 7.70 and 7.64 can be attributed to BB, and δ = 8.01, 7.93 and 7.74 to CB. Since the chemical shift at rt is the weighted mean of all of these conformers, the H_a proton signal of CB is δ = 8.01. Therefore, the aromatic protons can be assigned as follows: δ 8.01 (H_{a2}, CB), 7.93 ($H_{b1'}$, CB), 7.74 (H_{b2}, CB), 7.70 (H_{b1}, BB), and 7.64 (H_{a1}, BB). The proportion of the two conformers is estimated to be BB : CB = 1 : 1 on the basis of the ^{1}H NMR integrals of these peaks. Therefore, the BB and CB

Table 1 Calculated relative thermodynamic stabilities (kcal mol^{-1}, 25 °C)

	1BB	1CB	1CC
B3LYP/6-311G*[a]	0.00	1.00	2.65

[a] A zero-point vibrational correction has been made. The calculated absolute energies for **1BB**, **1CB**, and **1CC** are −762.2570023, −762.2551618 and −762.252581 E_h, respectively. The zero-point vibrational energies for **1BB**, **1CB**, and **1CC** are 751287.3, 750644.1 and 750762.8 J mol^{-1}, respectively. These energies are scaled by 0.9804.

conformers have the same stability. At the coalescence temperature of −55 °C, the free energy of activation $\Delta G^{\ddagger}$ is calculated to be 10.4 kcal mol^{-1}.

Theoretical calculations

It is known that theoretical MO calculations are effective methods for predicting the relative thermodynamic stabilities of conformers and their dynamic processes,[1,12] particularly in processes which are inaccessible to observation because of low energy barriers on the NMR time-scale.

Geometry optimizations and calculations of the relative thermodynamic stabilities (kcal mol^{-1}, 25 °C) of the three conformers of pyridinophane **1** (**1BB**, **1CB** and **1CC**) were performed as *ab initio* (DFT)[13] MO calculations in Gaussian 94.[14] The basis set used was DFT/B3LYP/6-311G*. The zero-point energy correction was applied for the calculated energy.

The resultant relative thermodynamic stabilities of three conformers are listed in Table 1. *ab initio* Calculation predicts the stabilities to be in the following order: BB > CB > CC. The estimated energy difference (1.00 kcal mol^{-1}) between the BB and CB conformers by the DFT/B3LYP method is in good agreement with the experimental result (*ca.* 0 kcal mol^{-1}).

X-Ray crystallographic analysis

The crystal structures of **1** and **6** were determined by X-ray diffraction crystallographic study. Single crystals of **1** and **6** were obtained by the slow evaporation of their solutions in MeOH. The crystallographic parameters of **1** and **6** are listed in Table 2. The ORTEP drawing and crystal packing diagrams of **1** and **6** are shown in Figs. 2 and 3, respectively.

In the case of **1**, three kinds of intermolecular hydrogen bonds are formed, H(9) ··· N(3) 2.42 Å, H(8) ··· N(2) 2.31 Å and H(3) ··· N(1) 2.64 Å (Fig. 2b and Table 3). As a result, **1** forms pairs with the pyridine rings facing each other, and the pairs are linked by the hydrogen bond between the bridging amine nitrogen atom and the amine hydrogen atom. This hydrogen-bonding network may lead to the relatively high melting point 254.0–256.5 °C. In order to form the latter hydrogen bond, the –CH_2NCH_2– bridges must be disordered, because if the all the bridges assume a chair conformation, no hydrogen bonds can be formed. Therefore, compound **1** assumes CC and CB conformations in the crystalline state at −180 °C, and the population is estimated to be CC : CB = 67 : 33. This result differs from that obtained by the VT NMR study and *ab initio* calculations, presumably due to crystal lattice energy and the above-mentioned hydrogen-bonding network.

The pyridinophane moiety of **6** adopts a CB conformation. The intermolecular contacts fall within the van der Waals radius at two positions: H(2) ··· N(1) 2.59 Å and H(7) ··· O(4) 2.48 Å (Fig. 3a and Table 3). Compound **6** aligns in a head-to-tail manner to form a columnar structure in its crystals.

Conclusion

The title compound, 2,11-diaza[3.3](3,5)pyridinophane **1**, was synthesized in three steps from 3,5-lutidine in an overall yield of

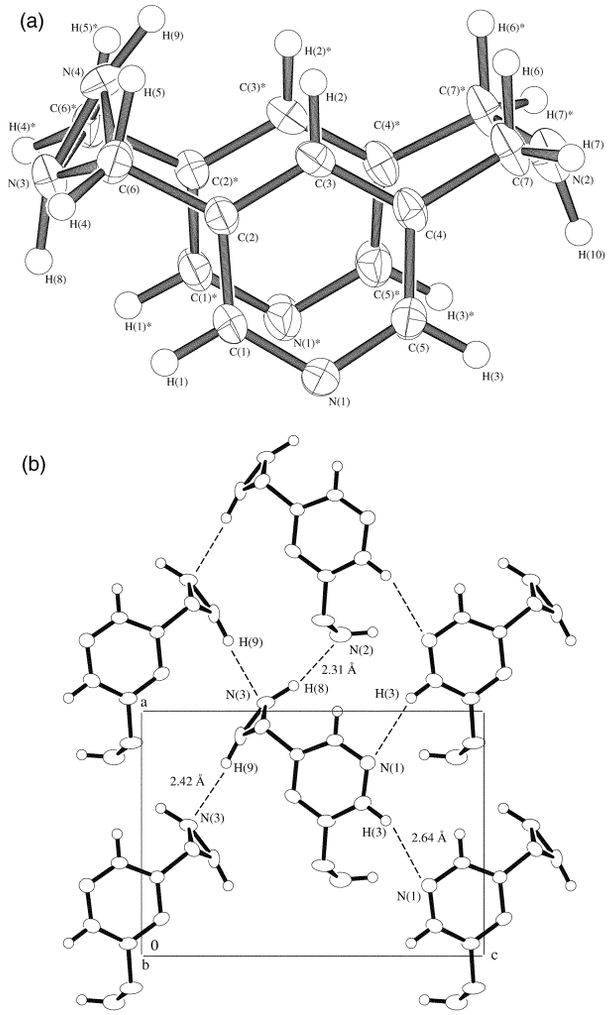


Fig. 2 (a) ORTEP drawing of **1** at 50% probability. One side of the bridge is disordered, N(3), H(8) (chair) and N(4), H(9) (boat). The population is estimated to be CC : CB = 67 : 33. (b) Packing diagram of **1** viewed along the *b* axis. Three kinds of hydrogen bonds [H(9) ··· N(3) 2.42 Å, H(8) ··· N(2) 2.31 Å and H(3) ··· N(1) 2.64 Å] are indicated by broken lines.

6%. A VT ^{1}H NMR study in CD_2Cl_2 indicated that the BB and CB conformers have almost the same stabilities, and *ab initio* MO calculations support this result. The free energy barrier $\Delta G^{\ddagger}$ for the bridge flipping (BB ⇌ CB) is estimated to be 10.4 kcal mol^{-1} (T_c = −55 °C), and the value is comparable to that of 2,11-diaza[3.3]metacyclophane **3** (10.8 kcal mol^{-1}, T_c = −40 °C), but slightly higher than that of 2,11-diaza-[3.3](2,6)pyridinophane **2** (9.9 kcal mol^{-1}, T_c = −57 °C). In contrast, **1** adopts CC and CB conformations in the solid state at −180 °C, mainly as a result of a characteristic intermolecular hydrogen-bonding network.

Four nitrogen lone pairs of electrons of 2,11-diaza[3.3]-(2,6)pyridinophane **2** are convergently directed and form metal complexes with Cu(II),[2a] Ni(II),[2b] Co(II),[2b] and Fe(II)[2c] ions. In contrast, [3.3](3,5)pyridinophane **1** has two types of nitrogen donor atoms: the pyridine nitrogen and the amino nitrogen in the bridge. Therefore, we can expect that this bireceptor molecule should form transition metal complexes at two donor sites, a study of which is in progress and the results will be reported elsewhere.

Experimental

General

^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 and 68 MHz for ^{1}H and ^{13}C, respectively), a JEOL JNM-AL300

Table 2 Crystal data for **1** and **6**[a]

	1	**6**
Formula	$C_{14}H_{16}N_4$	$C_{28}H_{28}N_4O_4S_2$
Formula weight	240.31	548.67
Crystal system	Orthorhombic	Orthorhombic
Space group	P_{nma} (no. 62)	$P2_12_12_1$ (no. 19)
a/Å	8.1751(4)	20.487(1)
b/Å	12.6839(9)	20.6726(8)
c/Å	11.4135(7)	6.1558(3)
Volume/Å^3	1183.5(2)	2607.1(2)
Temperature/K	93	296
Z value	4	4
D_{calc}/g cm^{-3}	1.349	1.398
μ(Mo-Kα)/cm^{-1}	0.84	2.47
Reflections measured	Total: 10318	Total: 12704
	Unique: 1421 (R_{int} = 0.067)	3324 (R_{int} = 0.056)
Number of variables	91	344
R	0.056	0.044
R_w	0.131	0.141
GOF	0.85	1.02
Number of reflections used in refinement for $I > 2.0\sigma(I)$ data	637	1540

[a] All hydrogen atoms were placed by calculation but not refined.

Table 3 Hydrogen bond and intermolecular contact data for **1** and **6**[a]

D–H ··· A[b]	D–H	H ··· A	D ··· A	∠D–H ··· A
Compound **1**				
N(4)–H(9) ··· N(3)^{i}	1.01	2.42	3.428(10)	177
N(3)–H(8) ··· N(2)^{ii}	1.08	2.31	3.367(5)	164
C(5)–H(3) ··· N(1)^{iii}	0.95	2.64	3.547(3)	160
Compound **6**				
C(3)–H(2) ··· N(1)^{iv}	0.95	2.59	3.483(8)	155
C(7)–H(7) ··· O(4)^{v}	0.97	2.48	3.415(8)	163

[a] Distances are given in Å; angles in deg. [b] D = donor, A = acceptor; i = $x - \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} - z$; ii = $1 + x, y, z$; iii = $x - \frac{1}{2}, y, \frac{3}{2} - z$; iv = $x, y, 1 + z$; v = $x, y, z - 1$.

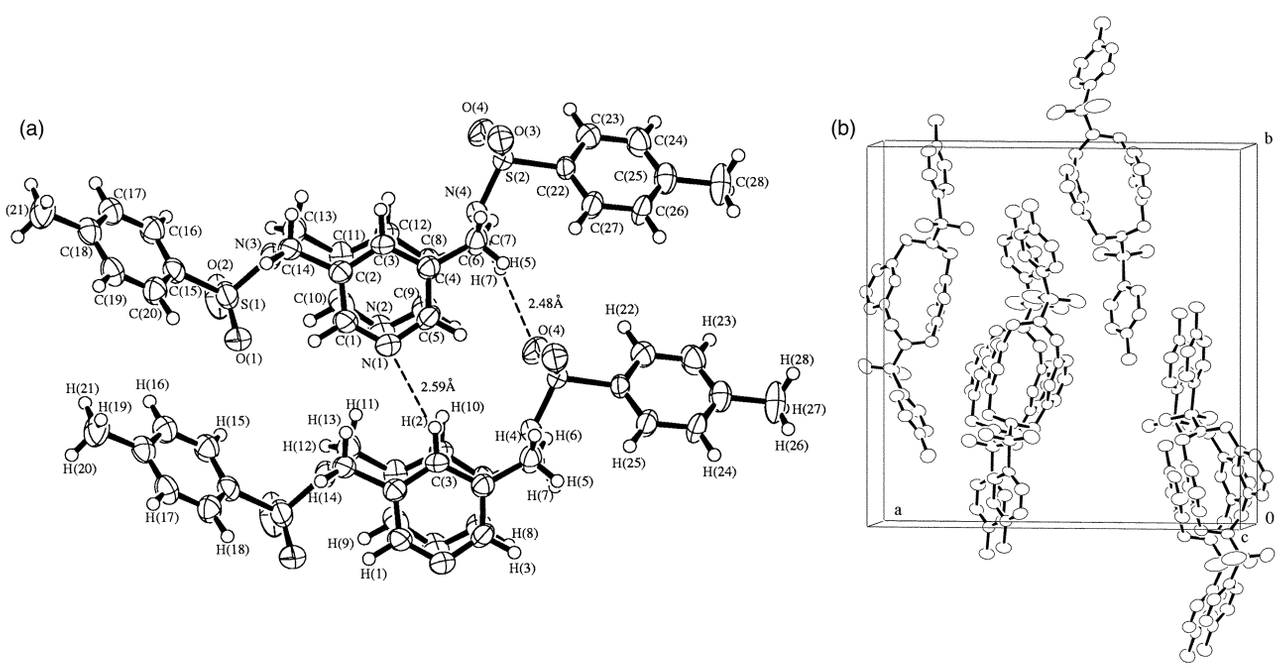


Fig. 3 (a) ORTEP drawing of a pair of molecules of **6** at 50% probability. Intermolecular contacts are indicated by broken lines. (b) Crystal packing diagram of **6** viewed along the *c* axis.

(300 and 75 MHz for ^{1}H and ^{13}C, respectively) and a Bruker DRX600 (600 MHz for ^{1}H) spectrometer in $CDCl_3$ unless otherwise noted, and chemical shifts are reported as δ values in ppm relative to the internal standard of TMS. FAB mass spectra were obtained with a JEOL JMS-SX/SX 102A with *m*-nitrobenzyl alcohol as a matrix. Melting points were measured on a Yanaco micro melting point apparatus MP-S3, and are uncorrected. Elemental analyses were carried out by the

Service Centre of the Elementary Analysis of Organic Compounds affiliated to the Faculty of Science, Kyushu University. Analytical thin layer chromatography (TLC) and column chromatography were performed using silica gel 60 F_{254} (Merck) and silica gel 60 (Merck, 40–63 mm or 60–200 mm), respectively. DMF was dried with 4 Å molecular sieves. 3,5-Bis(chloromethyl)pyridine **5** was obtained by chlorination of 3,5-lutidine in a procedure similar to a literature method.[6]

X-Ray crystallographic study ‡

All measurements were made on a Rigaku R-AXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The crystal structure was solved by the direct method SIR92[15] and expanded using DIRDIF94.[16] The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed by calculation but not refined. All the computations were performed using teXsan.[17]

Synthesis of *N*,*N*′-ditosyl-2,11-diaza[3.3](3,5)pyridinophane (6)

A 50 ml of DMF solution of chloromethyl compound **5** (1.79 g, 10.1 mmol) and toluene-*p*-sulfonamide (1.73 g, 10.1 mmol) was added dropwise to a suspension of NaH (1.2 g, 50 mmol) in 200 ml of DMF over a period of 25 min. at rt. The mixture was stirred overnight while the color of the solution changed from yellow to black. The DMF was removed under reduced pressure, and a small amount of water was added to the residue. Then the mixture was extracted with CH_2Cl_2, and the combined organic layer was dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give **6** as pale yellow crystals (650 mg, 23%). Compound **6**: mp 277.8–279.5 °C; an analytical sample was recrystallized from MeOH (Found: C, 61.05; H, 5.23; N, 10.33%. $C_{28}H_{28}N_4O_4S_2$ requires C, 61.29; H, 5.14; N, 10.21%). ^{1}H NMR ($CDCl_3$, 270 MHz) 7.99 (d, J = 1.65 Hz, 4H, Py), 7.84 (d, J = 8.24 Hz, 4H, Tosyl), 7.68 (s, 2H, Py), 7.44 (d, J = 8.58 Hz, 4H, Tosyl), 4.39 (s, 8H, –CH_2NCH_2–), 2.50 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 68 MHz) 148.8, 144.3, 139.9, 135.7, 130.7, 130.3, 127.2, 51.9, 21.6; FABMS *m*/*z* 549.20.

Synthesis of 2,11-diaza[3.3](3,5)pyridinophane (1)

To a 50 ml round-bottomed flask, which was placed in an ice bath, were added successively **6** (569 mg, 1.04 mmol) and conc. sulfuric acid (10 ml) slowly. The mixture was heated for 2 h at 110 °C with stirring. Then the reaction vessel was placed in an ice bath and made alkaline by the addition of aqueous sodium hydroxide solution. The resulting solution was continuously extracted with CH_2Cl_2 for 24 h. The extracted CH_2Cl_2 solution was evaporated under reduced pressure to give a pale yellow solid (220 mg, 87%). Compound **1**: mp 254.0–256.5 °C; an analytical sample was recrystallized from EtOH (Found: C, 69.91; H, 6.68; N, 23.20%. $C_{14}H_{16}N_4$ requires C, 69.97; H, 6.71; N, 23.31%). ^{1}H NMR ($CDCl_3$, 270 MHz) 7.89 (d, J = 1.65 Hz, 4H), 7.83 (s, 2H), 3.93 (s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) 148.1, 148.0, 134.4, 52.3; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{17}N_4$ (M^+ + H) 241.1450, found 241.1453.

Deuteration of 2,11-diaza[3.3](3,5)pyridinophane (1)

A mixture of **1** (8.4 mg, 0.03 mmol) and D_2O (0.5 ml, 99.8% D) was sealed in a glass tube, and the tube was heated at 200 °C for 4 days. The resultant solution was made alkaline with small amounts of aqueous sodium hydroxide solution, and extracted several times with CH_2Cl_2. The combined organic layer was evaporated to give a white powder (2.3 mg). The ratios of the ^{1}H NMR integrals of the aromatic and benzylic proton signals varied from H_a : H_b : H_{bz} = 2.0 : 4.0 : 8.0 to 2.0 : 2.3 : 6.0.

‡ CCDC reference numbers 173247 and 173248. See http://www.rsc.org/suppdata/p2/b2/b200402j/ for crystallographic files in .cif or other electronic format.

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