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SYNTHESIS AND STRUCTURAL STUDIES OF [n](2,4)PYRIDINOPHANE RING SYSTEM[1,2]

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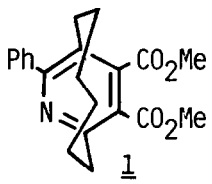
Summary: The facile synthesis of [n](2,4)pyridinophane ring system (n = 9-6) was accomplished by the reaction of N-(1-phenylvinyl)iminophosphorane with cyclic α,β-unsaturated ketones. The chain flipping was studied by ^{1}H NMR spectra at various temperatures.

The chemistry of strained and bridged aromatic compounds of cyclophane and heterophane has received a lot of attention in recent years.[3] The most interesting aspects of these compounds are the correlation of the aromaticity with the distortion of the aromatic ring and the static and dynamic conformation of the oligomethylene chain.[4-9] We previously studied the synthesis and spectroscopic properties of [6](2,5)pyridinophane derivative **1** which contains one of the most deformed pyridine rings.[6] The metapyridinophanes, incorporating the smallest chain so far reported, are [6](2,4)pyridinophanes **2**,[7a] the benzo-derivative **3**[7b,c] and [6](2,6)pyridinophane **4**.[9a] Since the compounds **2** and **3** have a halogen substituent, they do not seem appropriate for a study on the flipping of the hexamethylene bridge.[5a] We recently reported a facile preparation of pyridine derivatives by the reaction of N-vinyliminophosphorane with α,β-unsaturated ketones.[10] In this connection, we will describe here a simple synthesis and structural studies of phenyl-substituted [n](2,4)pyridinophanes (n = 9-6).

Synthesis of [n](2,4)pyridinophanes **9a-c**[11] (n = 9-7) was performed by the reaction of N-(1-phenylvinyl)iminotriphenylphosphorane **5**[10] with **6a-c**[12] in anhydrous benzene under reflux in the presence of Pd/C as a dehydrogenating reagent. In the reaction of **5** with **6d**[12], the intermediate **8d** was treated with DDQ followed by aqueous NaOH to give [6](2,4)pyridinophane **9d**.[11] The reaction conditions and the yields of the products are summarized in Table 1. The structures of the products were unequivocally characterized from their spectral data.[11] The postulated reaction pathways for the present reactions are shown in Scheme 1. The Michael addition of the iminophosphorane **5** to the β-carbon atom of **6a-d** and following hydrogen transfer gives **7a-d**. The compounds **7a-d** then undergo intramolecular aza-Wittig reaction to produce dihydropyridine derivatives **8a-d**. The dehydrogenation of **8a-c** with Pd/C results in the formation of **9a-c**. In the case of **8d**, DDQ instead of Pd/C was required for dehydrogenation, probably because of a large strain of **9d**. The compounds **10c,d** could originate from the



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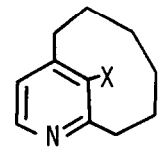
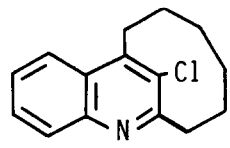


2 X = Cl, Br



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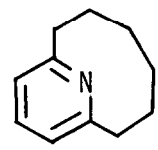

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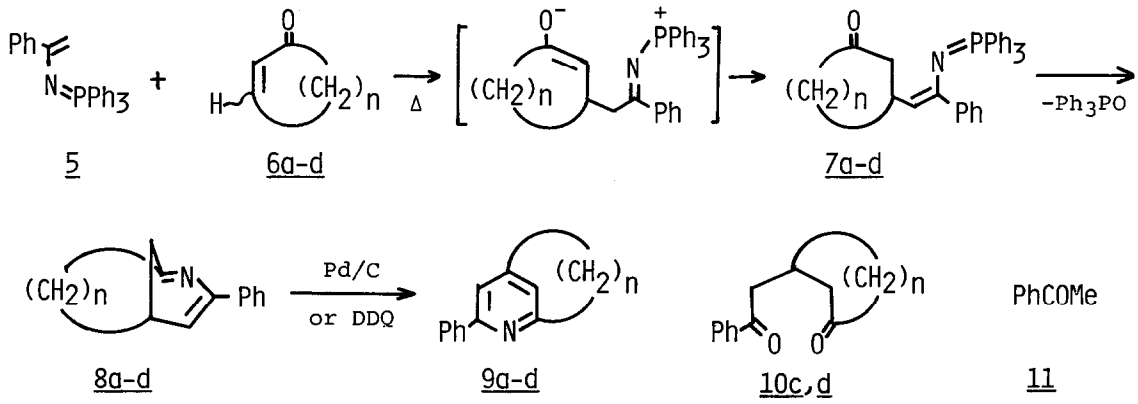

Scheme 1. a: n = 9, b: n = 8, c: n = 7, d: n = 6

Table 1. Reaction of N-(1-phenylvinyl)iminotriphenylphosphorane **5** with cyclic α,β-unsaturated ketones **6a-d**[a]

		Conditions			Products (yield/%)			Recovery (%)
Entry	**6**	n	Time/h	Oxidant	**9**	**10**	**11**[d]	**2**
1	**6a**	9	48	Pd/C[b]	68	0	24	21
2	**6b**	8	48	Pd/C[b]	47	0	12	23
3	**6c**	7	48	Pd/C[b]	69	3	26	7
4	**6d**	6	96	DDQ[c]	23	2	32	20

a. 1.5 molar equivalent amounts of **5** were used for all the reactions. b. 4 mol% to **5a-d** c. 1.0 molar equivalent amount of DDQ was added after unreacted **5** was removed by column chromatography. d. Acetophenone derives from hydrolysis of **5** under workup conditions.

hydrolysis of the intermediates **7c,d** and/or **8c,d** under workup conditions.

The ^{1}H NMR spectral data of **9a-d** are summarized in Table 2. A characteristic feature of the ^{1}H NMR of **9a-c** is the equivalence of geminal protons at the 'benzylic' positions, and these signals appear as a couple of triplets. This is indicative of a rapid flipping of the oligomethylene chain of **9a-c** at room temperature (cf. Fig. 1). The ^{1}H NMR spectrum of **9c** at low temperatures (400 MHz) clarified that the proton signal (δ -0.16) of H_{4x} and H_{4y} disappeared even at 20 °C, and H_{4x} in conformer **A** (or H_{4y} in **B**) reappeared at δ -1.45 (-60 °C) as 1H intensity with a clear coupling pattern. The counterpart at lower-field was hidden behind the signals of other aliphatic protons. Furthermore, the benzylic protons were also separated and appeared as four independent signals (δ 3.42 and 2.74 for H_7, δ 2.92 and 2.54 for H_1). These observations suggested that each geminal proton was located in a different environment and the flipping of the heptamethylene chain was then frozen in the NMR time scale at -60 °C. The energy barrier ($\Delta G^{\ddagger}_{c}$) of the conformational change between **A** and **B** (Fig. 1) was estimated to be

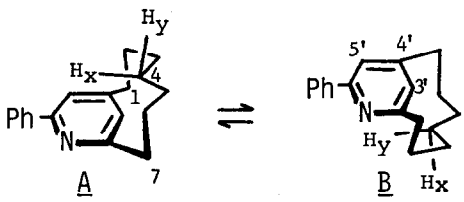

Fig. 1. The flipping of the heptamethylene chain of **9c**.

Table 2. The ^{1}H NMR spectral data of **9a–d** in $CDCl_3$ at room temperature[a]

Compound		Aromatic		Benzylic		Methylene Bridge		
9	n	$H_{3'}$	$H_{5'}$	H_n	H_1	H_{n-1} - H_2		
9a[b]	9	7.11	7.30	2.94 (2H, t)	2.69 (2H, t)	1.75 (4H)	1.16 (6H)	0.90 (4H)
9b[b]	8	7.12	7.27	2.86 (2H, t)	2.62 (2H, t)	1.55 (4H)	1.26 (4H)	0.63 (4H)
9c[c]	7	7.32	7.26	2.90 (2H, t)	2.69 (2H, t)	1.41 (8H)	-0.16 (2H)	
9d[c]	6	7.19	7.09	3.09 (1H, ddd)	2.79 (1H, ddd)	1.82 (2H)	1.54 (1H)	1.21 (3H)
				2.71 (1H, ddd)	2.63 (1H, ddd)	0.70 (1H)	0.01 (1H)	

a. Chemical shifts are given in δ (ppm) relative to internal TMS.

b. Hitachi R-90H (90MHz) c. JEOL GSX400 (400MHz)

12-13 kcal/mol (Tc, +20 °C), which is close to that of [7]metapyridinophane (11.5 kcal/mol, Tc = -28 °C).[5a]

On the contrary, four benzylic protons in **9d** at room temperature exhibited different chemical shifts, suggesting that the flipping of the hexamethylene chain is frozen. An increase in temperature above 150 °C (Tc, 90 MHz) provided clear indication for coalescence of the benzylic protons. Consequently, $\Delta G^{\ddagger}_c$ for the flipping of the hexamethylene chain of **9d** (**C,D** ⇌ **E,F** in Fig. 2) was estimated to be 21-22 kcal/mol. This value seems to be higher than that of [6]metacyclophane (17.4 kcal/mol, Tc = 76.5 °C).[5a] The larger value of $\Delta G^{\ddagger}_c$ for **9d** as compared to that of **9c** clearly indicates the higher degree of strain of **9d**.

Absence of signals above 0 ppm suggests that the structure of **9d** is not fixed in either conformer **C** or **D** (**E** or **F**) at room temperature and a rapid equilibrium between them is set up by pseudorotation (Fig. 2). Two proton signals at high-field (δ 0.70 and 0.01) disappeared at -10 °C and reappeared at δ -1.26 (0.33H) and -1.47 (0.67H) at -90 °C, either of which is assigned to H_{4x} in **C** or H_{3x} in **D** (H_{4y} in **E** or H_{3y} in **F**). The counterparts at lower-field were not determined because they are overlapped with other signals of aliphatic protons. Observation of the two conformers elucidated that the pseudorotation between **C** and **D** (**E** and **F**) is frozen at this temperature. A detailed kinetic study of the pseudorotation is now underway.

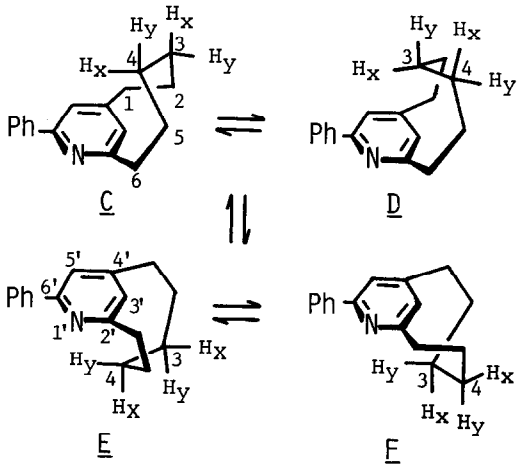

Fig. 2. Conformational equilibrium of **9d**: the pseudorotation (**C** ⇌ **D**, **E** ⇌ **F**) and the flipping (**C,D** ⇌ **E,F**).

The chemical shifts of aromatic protons are helpful to examine the distortion of the aromatic ring of cyclophanes.[13] The downfield shift was observed in $H_{3'}$ of **9c**, being

Table 3. UV spectra of **9a–d** in EtOH

9	n	λmax (log ε) (nm)		
9a	9	210 (4.33)	248 (4.05)	281 (4.00)
9b	8	211 (4.37)	248 (4.10)	282 (4.04)
9c	7	211 (4.39)	249 (4.08)	285 (3.98)
9d	6	208 (4.44)	255 (4,04)	299 (3.89)

attributable to a steric compression between $H_{3'}$ and the methylene bridge.[5a] On the other hand, chemical shifts of $H_{3'}$ and $H_{5'}$ of **9d** appeared at higher field than those of **9c** reflecting the decrease of ring current of the strained pyridine ring.

The deformation of the pyridine ring is generally evaluated by the bathochromic shift of UV spectra. The significant ring strain of [6](2,4)pyridinophane derivative **9d** was reflected in the absorption maximum at 299nm longer by 18nm than that of **9a** (Table 3).

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