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STUDIES ON PYRIMIDINE-ANNULATED HETEROCYCLES: SYNTHESIS AND DYNAMIC PROPERTIES OF [n](2,4)-PYRIDINOPHANES (n = 11, 9, 8, 6)

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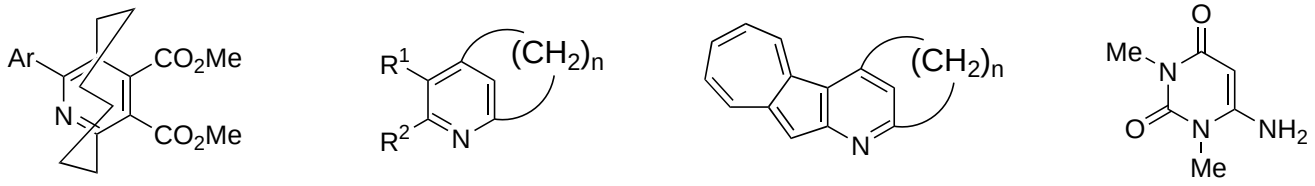
Abstract--A new short synthesis of the 1,3-dimethyluracil-annulated [n](2,4)pyridinophane ring system (n = 11, 9, 8, 6) (5,7-polymethylene-substituted pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones) consists of allowing 6-amino-1,3-dimethyluracil to react with cyclic α,β-unsaturated ketones. Structural studies of the compounds prepared were based on spectroscopic measurements and theoretical calculations. The ^{1}H and ^{13}C NMR spectra at various temperatures showed dynamic behavior for the oligomethylene chain of [6](2,4)pyridinophane derivative (**9d**). The energy barriers $\Delta G_c^{\ddagger}$ of the bridge flipping is *ca.* 20 kcalmol^{-1} (T_c, 150 °C). The lower-energy process of the oligomethylene in **9d** is the pseudorotation with $\Delta G_c^{\ddagger}$ being 10.1 kcalmol^{-1} (T_c, -30 °C). Two stable conformers of the hexamethylene bridge of annulated [6](2,4)pyridinophane (**9d**) were determined for the first time by low-temperature NMR spectroscopy and theoretical calculations. Furthermore, the first example of rearrangement observed in the dehydrogenation reaction of a 3,4-dihydro[5](2,4)pyridinophane derivative in the presence of DDQ suggested the large strain of the [5](2,4)pyridinophane ring system.

The remarkable chemical and physical properties of strained cyclophanes continue to fascinate many

chemists.[1-4] In the field of heterocyclic [n]paracyclophanes,[5,6] the smallest known member is [6](2,5)pyridinophane (**1**).[5] In the [n]metacyclophane series, the smallest known members thus far obtained are 3-halogeno-substituted [6](2,4)pyridinophanes,[7] [n](2,6)pyridinophane (n = 12 and 10-6),[8] [n](3,5)pyridinophanes (n = 9 and 7),[9] 3-chloro-substituted [6](2,4)quinolinophane.[10,11] Previously, we worked on a convenient preparation of [n](2,4)pyridinophane derivatives (**2**)[12,13] and azuleno-annulated [n](2,4)pyridinophane (**3**) (n = 9-6),[14] and studied their static and dynamic behaviors (Scheme 1). The synthesis consists of an enamine-alkylation process of vinyliminophosphorane, β-amino enones, and 2-aminoazulene with cycloalk-2-enones, respectively, subsequent condensation of the nitrogen moiety with the carbonyl function, and dehydrogenation. The utility of vinyliminophosphoranes as useful building blocks for the synthesis of aza-heterocycles has been demonstrated.[15] Regarding 6-amino-1,3-dimethyluracil (**4**), it undergoes many reactions with Michael acceptors and is a useful intermediate for synthesis of uracil-annulated heterocycles.[16] Investigation has now been made of the behavior of **4** with cycloalk-2-enone (**5a-e**) leading to 1,3-dimethyluracil-annulated [n](2,4)pyridinophanes (**9a-d**) (5,7-polymethylene-substituted pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones) and 6,7-pentamethylene-annulated



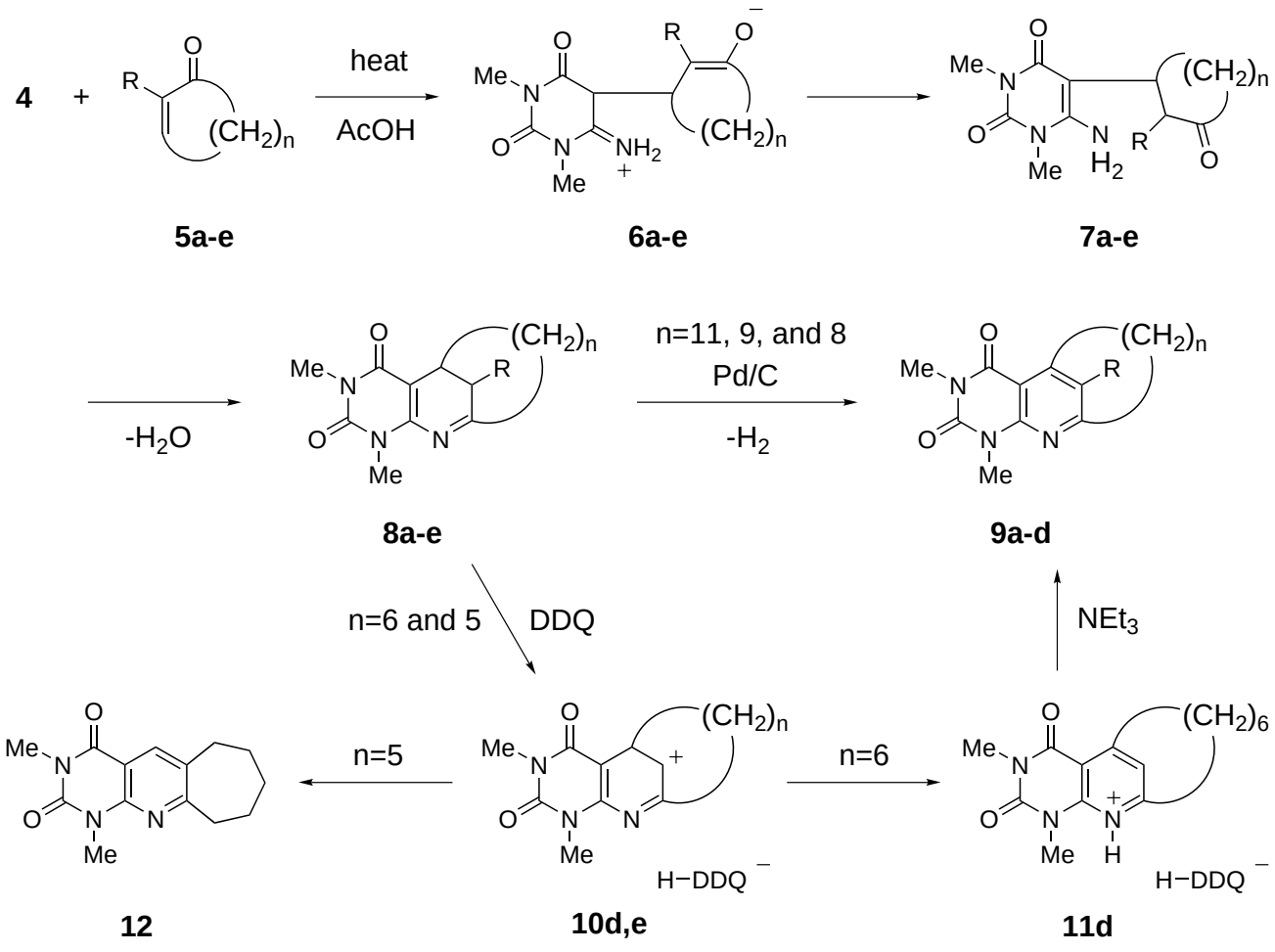
1 **2** (n=9-6) **3** (n=9-6) **4**

Scheme 1.

pyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**12**), and the study of the static and dynamic behaviors thereof. A further objective of this study is an attempted preparation of the first examples of [11](2,4)pyridinophane (**9a**) with restricted bridge-flipping due to the steric hindrance and [5](2,4)pyridinophane.

The compounds (**4**),[17] (**5a**),[18] (**5b-d**),[12] and (**5e**)[19] were prepared as described previously. In the earlier paper,[18] 2-methylcyclotetradec-2-enone was prepared as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 2/1. However, attempted preparation and assignment of the ^{1}H NMR spectrum of the mixture suggested that the mixture consists of (*E*)-2-methylcyclotetradec-2-enone (**5a**) and (*E*)-2-methylcyclotetradec-3-enone (**5a'**) in a ratio of 2/1 (see EXPERIMENTAL). Thus, the mixture was used for the reaction with **4**.

The thermal reaction of 6-amino-1,3-dimethyluracil (**4**) with 2-methylcyclotetradec-2-enone (**5a**) in AcOH in the presence of a catalytic amount of a dehydrogenating agent (10% Pd/C) under heating at 117 ℃ afforded [11](2,4)pyridinophane derivative (**9a**) along with unidentified material (Scheme 2). The reaction conditions and the yield of the products are listed in Table 1 (Run 1). Likewise, the reaction of **4** with cycloalk-2-enones (**5b,c**) under similar conditions gave [n](2,4)pyridinophane derivatives (**9b,c**) in good yields (Table 1, Runs 2 and 3). Although the reactions of **4** with **5d,e** under these conditions gave no [n](2,4)pyridinophane derivatives, the reactions of **4** with **5d,e** and subsequent treatment of the reaction mixtures with DDQ resulted in the formation of [6](2,4)pyridinophane (**9d**) and 6,7-pentamethylene-substituted pyrido[2,3-*d*]pyrimidine (**12**) along with a trace amount of unidentified material (Table 1, Runs 4 and 5), respectively. The postulated reaction pathways for the formation of [n](2,4)pyridinophanes (**9a-d**) and pyrido[2,3-*d*]pyrimidine (**12**) are also shown in Scheme 2. Enamine alkylation of **4** to the β-carbon atom of **5a-e** gives zwitterions (**6a-e**). The following tautomerization in **6a-e** regenerates the



a: R=Me, n=11; **b**: R=H, n=9; **c**: R=H, n=8;
d: R=H, n=6; **e**: R=H, n=5

Scheme 2.

β-amino enone moiety in **7a-e**. The enamine intermediates (**7a-e**) undergo intramolecular condensation to produce dihydropyridines (**8a-e**). Dehydrogenation of **8a-c** by 10% Pd/C results in the formation of [n](2,4)pyridinophane (**9a-c**). In the case of the constrained **8d,e** (n = 6 and 5), DDQ is required for the hydride abstraction to give the intermediates (**10d,e**). The deprotonation of the intermediate (**10d**) gives **11d**, which reacts with NEt_3 to yield [6](2,4)pyridinophane (**9d**). On the other hand, the intermediate (**10e**) (n = 5) is very constrained and does not undergo deprotonation, but instead it undergoes 1,2-alkyl migration[20] to result in the formation of pyrido[2,3-*d*]pyrimidine (**12**) in low yield. Furthermore, the intermediates (**7a,e**) experience large steric hindrance of the methyl group for **7a** and the short methylene bridge for **7e** (n = 5) in the condensation process giving **8a,e**. Thus, **7a** as well as **7e** seem to collapse to give unidentified materials. The reaction of **4** with **5a** afforded an unidentified by-product, which corresponds to a dehydrogenated product of a condensate arising from **4** and **5a** in a ratio of 1/2, in 12% yield based on **4** used [mp 99-100 °C (from EtOH); MS (*m/z*) 597 (M^+, 26%), 386 (100). *Anal.* Calcd for $C_{36}H_{59}N_3O_4$: C, 72.32; H, 9.95; N, 7.03. Found: C, 72.21; H, 10.06; N, 6.98.]. Thus, the reactions of **4** with **5a,d,e** were carried out by using **4** and **5a,d,e** in a ratio of 1/1.2 as summarized in Table 1. The reaction of **4** with **5b,c** proceeded smoothly by using **5b,c** in excess amounts (Table 1). The structures of compounds (**9a-d**) were deduced from their spectral data and elemental analyses. All the ^{1}H NMR spectra of the compounds correlate well with each other and are in good accordance with the proposed structures (Table 2). The compound (**12**) is known and the structure was assigned on the basis of the comparison of the physical data with those reported in the literature.[16d]

Table 1. Results for the reaction of uracil (**4**) with cycloalk-2-enones (**5a-e**)

Run	Cycloalk-2-enone	Molar ratio of **5a-e** / **4**	Reaction time (/h)	Product (yield/%)
1	**5a**[a]	1.2[b]	15	**9a** (14)
2	**5b**	2.1	6	**9b** (91)
3	**5c**	2.0	18	**9c** (82)
4	**5d**	1.2[b]	4.5	**9d** (48)
5	**5e**	1.2[b]	6	**12** (3.4)

a. A mixture of **5a** and **5a'** in a ratio of 2/1 was used (cf. EXPERIMENTAL). b. Molar ratio of **5a,d,e**/**4** (2.0) did not improve the yields of **9a,d** and **12**.

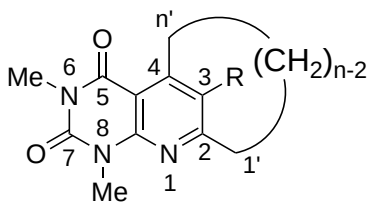


Figure 1.

The ^{1}H NMR spectral data for [n](2,4)pyridinophanes (**9a-d**) are

Table 2. ^{1}H NMR spectral data of [n](2,4)pyridinophanes (**9a-d**)[a]

Compd	Pyridine δ H3	Benzylic δ H1' and δ Hn'	Remaining methylene bridge and methyl group
9a	2.38[b]	2.74 (1H, ddd, *J*=12.8, 6.5, 3.5), 2.75 (1H, ddd, *J*=13.3, 9.0, 5.4), 3.23 (1H, ddd, *J*=13.3, 6.1, 4.4), 4.55 (1H, ddd, *J*=12.8, 10.4, 3.8)	0.49-0.59 (1H, m), 0.68-0.92 (3H, m), 0.95-1.30 (10H, m), 1.49-1.59 (1H, m), 1.67-1.79 (3H, m), 3.45 (3H, s), 3.70 (3H, s)
9b	7.03	2.87 (2H, t, *J*=6.4), 3.33 (2H, t, *J*=6.4)	0.80-0.88 (2H, m), 0.96-1.09 (4H, m), 1.09-1.22 (4H, m), 1.76-1.86 (4H, m), 3.45 (3H, s), 3.71 (3H, s)
9c	7.07	2.80 (2H, t, *J*=6.2), 3.30-3.40 (2H, m)	0.69-0.82 (4H, m), 1.13-1.23 (2H, m), 1.23-1.31 (2H, m), 1.59-1.74 (4H, m), 3.45 (3H, s), 3.71 (3H, s)
9d[c]	7.10	2.63 (1H, ddd, *J*=13.0, 7.1, 5.4, H1'), 2.65 (1H, ddd, *J*=12.5, 8.4, 6.3, H6'), 3.02 (1H, dt, *J*=13.0, 7.5, H1'), 4.24 (1H, dt, *J*=12.5, 4.9, H6')	0.07 (1H, br s, H3'x), 0.56 (1H, br s, H4'x), 1.17-1.33 (3H, m, H3'y, H4'y, H5'), 1.40-1.50 (1H, m, H2'), 1.78-1.92 (2H, m, H2', H5'), 3.38 (3H, s, Me), 3.64 (3H, s, Me)
9d (**A**)[c,d]	7.05	2.37 (2H, m, H1', H6'), 3.19 (1H, m, H1'), 4.36 (1H, m, H6')	-1.63 (1H, br s, H3'x), 0.63 (1H, m, H5'), 0.90 (1H, br s, H4'y), 1.31 (1H, br s, H3'y), 1.61 (1H, br s, H2'), 1.80 (1H, m, H2'), 1.88 (2H, m, H4'x, H5'), 3.30 (3H, s, Me), 3.53 (3H, s, Me)
9d (**B**)[c,d]	7.05	2.68 (2H, br s, H1'), 2.90 (1H, m, H6'), 3.75 (1H, m, H6')	-1.52 (1H, br s, H4'x), 0.63 (1H, m, H2'), 0.97 (1H, br s, H3'y), 1.31 (1H, br s, H4'y), 1.61 (1H, br s, H5'), 1.69 (1H, br s, H5'), 1.80 (1H, m, H3'x), 1.88 (1H, m, H2'), 3.29 (3H, s, Me), 3.55 (3H, s, Me)

a. Recorded on a 500 MHz spectrometer in $CDCl_3$. b. Signal of methyl group. c. Recorded in CD_2Cl_2. d. Recorded at -95 °C.

summarized in Table 2 (see the convenient, but not systematic numbering of the methylene illustrated in Figure 1). Since no uracil-annulated pyridinophanes have been reported, study of the dynamic behaviors of **9a-d** is interesting. A characteristic feature of **9b,c** is the equivalence of the geminal hydrogens at the 'benzylic' positions H1' and Hn' (Figure 1), where the signals appear as a couple of triplets. This feature is indicative of a rapid flipping of the methylene bridge of **9b,c** at room temperature; spectral properties similar to those of **9b,c** were also observed for [n](2,4)pyridinophane derivatives (n = 9-7),[12-14] which undergo rapid flipping. In contrast, the four benzylic hydrogens of **9a,d** exhibited different chemical shifts at room temperature (Table 2), suggesting that the flipping of the undecamethylene chain and hexamethylene chain is frozen in the NMR time scale. In the case of **9a** in DMSO-d_6, an increase in temperature around 150 ℃ provides no indication of the spectral change. These feature indicates that **9a** does not undergo a bridge flipping of the undecamethylene chain even at 150 °C, because of the steric hindrance due to the introduction of the methyl group at the C3 position of the pyridine ring. Furthermore, the MM2, MNDO, AM1, and PM3 calculations suggest that [6](2,4)pyridinophane (**9d**) exists in two stable conformers **A** [**C**] and **B** [**D**] in Figure 2. The calculated total energy and the heats of formation ($\Delta H_f°$) obtained by several methods are listed in Table 3.

Table 3.Calculated energy (kcalmol^{-1}) for the optimized conformers (**A**) and (**B**) of **9d**

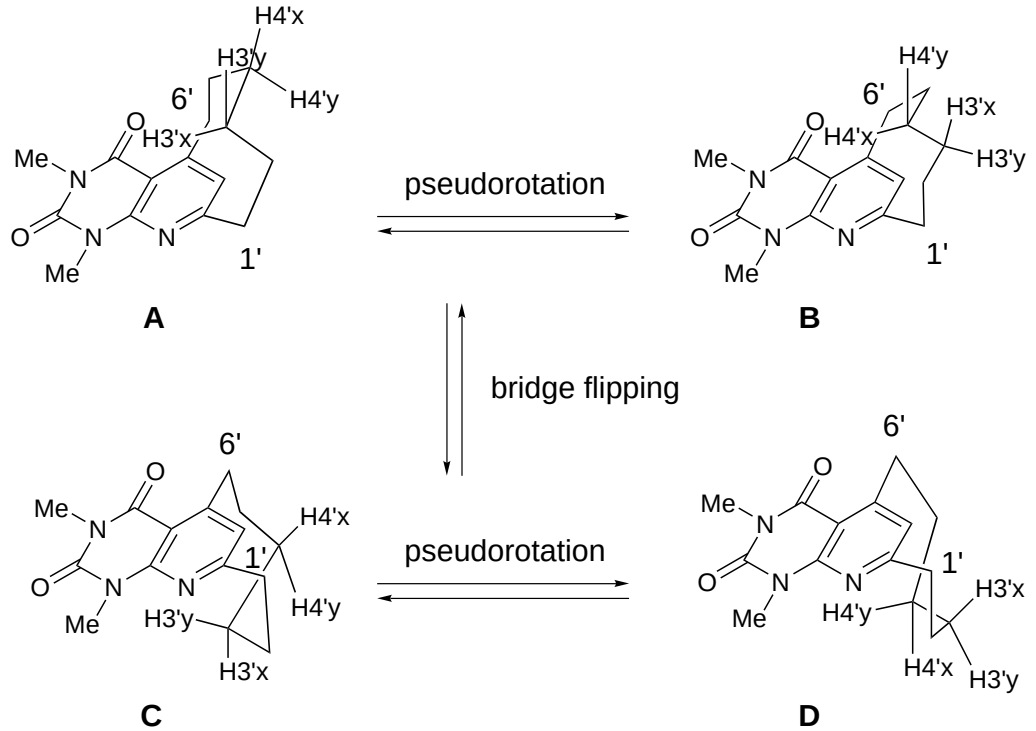
Method	Conformer **A**	Conformer **B**
MM2[a]	46.48	45.75
MNDO[b]	-31.64	-31.93
AM1[b]	-22.00	-22.53
PM3[b]	-51.66	-51.99

a. Total energy calculated by using MM2 force field CS Chem3D Pro Ver. 3.2 program. b. Heat of formation ($\Delta H_f°$) calculated by using MOPAC Ver. 6.12 program.

Regarding the assignment of the hydrogens and the carbons for hexamethylene bridge of **9d** at room temperature (Table 2 and 4), four geminal hydrogens at benzylic positions (H1' and H6') two pairs of signals (δ 2.63 and δ 3.02; δ 2.65 and δ 4.24 assigned by ^{1}H-^{1}H Cosy spectrum) appear at lower field than the remaining bridge hydrogens (H2'-H5'), because of the anisotropy effect of the pyridine ring. Generally, the benzylic hydrogens (H1') appear slightly lower field than the hydrogens (H6'), however, one of the hydrogens appearing as a couple of signals (δ 2.65 and δ 4.24) is shifted much lower field than a couple of signals appearing at δ 2.63 and δ 3.02. The low-field shift is probably due to the anisotropy effect of the carbonyl-oxygen at C5 position, thus, a couple of signals appearing at δ 2.65 and δ 4.24 is assigned as the hydrogens H6'. The remaining bridge hydrogens were assigned by ^{1}H-^{1}H Cosy

spectrum. In analogy with the previous studies of 6-phenyl[6](2,4)pyridinophane,[12] the signals for one of H3' (δ 0.07) and one of H4' (δ 0.56) were assigned to H3'x and H4'x for **A** and **B** [H3'y and H4'y for **C** and **D**], respectively, because of the anisotropy effect of the pyridine ring. The carbons of hexamethylene bridge were assigned by ^{1}H-^{13}C Cosy spectrum. Similarly, the signals of the hydrogens and the carbons for conformers (**A** [**C**]) and (**B** [**D**]) at -95 °C were assigned.

Then, ^{1}H NMR spectroscopy is conducted at various temperatures to clarify the dynamic behavior of **9d**. An increase in temperature to 150 °C (T_c, 270 MHz in DMSO-d_6) provides indication of the coalescence of the benzylic type protons H1' [δ ~2.50 and δ 3.06 (overlapping with the signal of DMSO)]. This feature indicates that **9d** undergoes bridge flipping of the hexamethylene chain [**A** (**B**) ⇄ **C** (**D**)] (Figure 2). Consequently, the $\Delta G_c^{\ddagger}$ value for the flipping was estimated to be *ca.* 20 kcalmol^{-1}. In addition, the conformation of **9d** is not fixed in either conformer **A** or **B** [**C** or **D**] (Table 3 and Figure 2) at room temperature and a rapid equilibrium between **A** and **B** [**C** and **D**] would exist due to the pseudorotation. Two proton signals (in CD_2Cl_2, Table 2) at δ 0.07 (δ_{av} of H3'x for **A** and **B** [δ_{av} of H3'y for **C** and **D**]) and δ 0.56 (δ_{av} of H4'x for **A** and **B** [δ_{av} of H4'y for **C** and **D**]) disappeared at -30 °C, and reappeared at δ -1.63 (H3'x for **A** [H3'y for **C**]) as of 0.59H intensity and δ -1.52 (H4'x for **B** [H4'y for **D**]) as of 0.41H intensity at -95 °C. The signals of the counterparts appear at δ 1.80 (H3'x for **B** [H3'y for **D**]) and δ 1.88 (H4'x for **A** [H4'y for **C**]), respectively. Thus, the conformer **A** [**C**] is slightly more stable than



9d

Figure 2.

Table 4. ^{13}C NMR spectral data of [6](2,4)pyridinophanes (**9d**) in CD_2Cl_2 at various temperatures[a]

Temp.	Conformer	C3	C1'	C2'	C3'	C4'	C5'	C6'	Remaining Signals
30 °C	---	125.9	37.3	31.0	26.8	28.3	31.4	33.4	28.2, 30.3, 104.7, 151.9, 152.0, 157.1, 162.2, 166.8
-95 °C	**A**	124.9	34.3	28.5	24.4	27.8	31.2	34.2	27.6, 29.7, 101.7, 150.1, 150.6, 155.1, 161.2, 167.2
	B	125.5	38.3	31.0	26.0	25.4	28.4	30.2	27.5, 29.8, 105.5, 150.7, 151.0, 157.4, 161.1, 164.3

a. Recorded on a 125.8 MHz spectrometer.

the conformer **B** [**D**]. At this temperature the pseudorotation also stopped. These findings are in accordance with the results found for 6-phenyl[6](2,4)pyridinophane, which shows similar phenomena in the dynamic ^{1}H NMR study.[12] Consequently, the energy barrier ($\Delta G_c^{\ddagger}$) for the conformational change (pseudorotation) between **A** and **B** [**C** and **D**] was estimated to be 10.1 kcalmol^{-1}, and the free energy difference (ΔG) between **A** and **B** [**C** and **D**] was estimated to be 0.13 kcalmol^{-1}, which does not seem to support the calculated values (Table 3).

Regarding $\Delta G_c^{\ddagger}$ values of the bridge flipping and pseudorotation for **9d**, the $\Delta G_c^{\ddagger}$ value for the bridge flipping of **9d** is slightly smaller than that of the corresponding value of 6-phenyl[6](2,4)pyridinophane ($\Delta G_c^{\ddagger}$ = 21-22 kcalmol^{-1}; T_c = 150 °C).[12] Furthermore, there is a slight difference between $\Delta G_c^{\ddagger}$ values for the pseudorotation of **9d** and that of the corresponding value of 6-phenyl[6](2,4)pyridinophane ($\Delta G_c^{\ddagger}$ = 9.8 kcalmol^{-1}; T_c = -30 °C).[12] Consequently, it is clarified that the flexibility of uracil-annulated [6](2,4)pyridinophane (**9d**) seems to be similar to the corresponding 6-phenyl[n](2,4)pyridinophane having the same value of n.[12]

The deformation of the aromatic rings of cyclophanes[21] and [n](2,4)pyridinophanes[12-14] is evaluated by the red-shift of the UV spectra. The UV spectra of pyridinophanes (**9a-d**) are

Table 5. UV spectral data of [n](2,4)pyridinophanes (**9a-d**)

Compd	n	λ_{max} (log ε) (MeCN)
9a	11	229 (4.54), 247 (3.87, sh), 317 (3.82), 324 (3.78, sh)
9b	9	227 (4.54), 249 (3.87, sh), 311 (3.84), 317 (3.81, sh)
9c	8	227 (4.55), 249 (3.84, sh), 310 (3.85), 316 (3.82, sh)
9d	6	229 (4.49), 255 (3.77, sh), 317 (3.83)

summarized in Table 5. The spectra of pyridinophanes (**9b**) and (**9c**) are similar, but the absorption maxima of pyridinophane (**9a**) seem to shift to a longer wave-length than those of **9b,c**, probably because of the methyl group at C3 position. On the other hand, the spectrum of **9d** shifts also to a longer wave-length than those of **9b,c**, because of the short hexamethylene bridge.[12,14]

In summary, synthesis of uracil-annulated [n](2,4)pyridinophanes (**9a-d**) and the dynamic behaviors of the pyridinophanes (**9a,d**) have been studied for the first time. The behavior of **9d** seems to be similar to that of the related [6](2,4)pyridinophane.[12] Furthermore, the DDQ-prompted hydride-abstraction reaction of the postulated intermediate (uracil-annulated 3,4-dihydro[5](2,4)pyridinophane) (**8e**) underwent 1,2-alkyl migration to result in the formation of 2,3-pentamethylene-substituted pyridine derivative (**12**), suggesting the high degree of the strain in a [5](2,4)pyridinophane ring system.

EXPERIMENTAL

IR spectra were recorded on a Horiba FT-710 spectrophotometer. UV-VIS spectra were recorded on a Shimadzu UV-3101PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270, a JEOL JNM-AL400, and a JEOL JNM-LA500 spectrometers using $CDCl_3$ (unless otherwise specified) as a solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard: *J*-values are given in Hz. MS spectra were run on a JEOL Automass 150 spectrometer. Mps were measured on a Yamato MP-21 apparatus and are uncorrected. The desired 6-amino-2,4-dimethyluracil (**4**),[17] (*E*)/(*Z*) mixtures of cyclododec-2-enone (**5b**) and cycloundec-2-enone (**5c**), (*Z*)-cyclonon-2-enone (**5d**),[12] and (*Z*)-cyclooct-2-enone (**5e**)[20] were prepared by the literature procedure. All the reactions were carried out under dry nitrogen atmosphere.

Preparation of (*E*)-2-methylcyclotetradec-2-enone (5a). To the solution of 2-methyl-3-morpholinylcyclotetradec-2-enone[18] (16.14 g, 52.5 mmol) in Et_2O (54 mL) was added $LiAlH_4$ (1.45 g, 38 mmol) by portions, and the mixture was refluxed for 3 h and cooled to rt. To this reaction mixture were added MeOH (4 mL) and 15% HCl (54 mL), and the mixture was stirred for 5 h, extracted with Et_2O, and the Et_2O extract was washed with saturated aqueous $NaHCO_3$ solution, brine, and dried over Na_2SO_4. After evaporation of the Et_2O, the residual oil (3-hydroxy-2-methylcyclotetradacanone) and *p*-TsOH•H_2O (280 mg, 1.47 mmol) were dissolved in toluene (100 mL), and the mixture was heated under reflux by using a Dean-Stark apparatus for 2 h. To the mixture was added H_2O (100 mL), and the mixture was

extracted with Et_2O and the Et_2O extract was dried over Na_2SO_4. After evaporation of the solvent, the residual oil was distilled to give a mixture of **5a** and (*E*)-2-methylcyclotetradec-3-enone (**5a'**) in a ratio of 2/1 (5.74 g, 49%): bp 118-125 ℃/1 torr (lit.,[18] 118-123 ℃/1 torr). Assignment of the ^{1}H NMR (400 MHz) spectrum of the mixture is accomplished as follows. For **5a**: δ 1.17-1.43 (m, overlapping), 1.52-1.75 (m, overlapping), 1.78 (3H, d, *J*=1.2), 2.31 (2H, q, *J*=7.3), 2.64 (2H, t, *J*=7.3), 6.69 (1H, tq, *J*=7.3, 1.2). For **5a'**: δ 1.13 (3H, d, *J*=6.8), 1.17-1.43 (m, overlapping), 1.52-1.75 (m, overlapping), 2.44-2.49 (4H or 5H, m), 5.32 (1H, dddd, *J*=15.1, 8.8, 1.5, 1.0), 5.55 (1H, dddd, *J*=15.1, 9.3, 5.4, 0.5).

General synthetic procedure for [n](2,4)pyridinophanes (9a-c). A mixture of 10% Pd/C (11 mg), 6-amino-2,4-dimethyluracil (**4**) (78 mg, 0.5 mmol) and cycloalk-2-enones (**5a-c**) in AcOH (0.5 mL) was heated under reflux for the period indicated in Table 1. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The resulting residue was separated by TLC on silica gel ($CHCl_3$) to give [n](2,4)pyridinophane derivatives (**9a-c**). The reaction conditions and the yields of the products are summarized in Table 1.

For 3-methyl[11](2,4)pyridinophane derivative (**9a**): colorless powder; mp 178-179 ℃ (from EtOH); ^{13}C NMR (125.8 MHz) δ 15.2, 24.1, 24.4, 24.5, 25.5, 26.0, 26.5, 26.6, 26.8, 27.1, 27.5, 28.5, 29.8, 36.2, 107.1, 126.4, 148.7, 151.5, 156.0, 162.2, 165.2; IR (KBr) 1704, 1661 cm^{-1}; MS (*m/z*) 357 (M^+, 60%), 233 (100). *Anal*. Calcd for $C_{21}H_{31}N_3O_2$: C,70.55; H, 8.74; N, 11.75. Found: C, 70.44; H, 8.97; N, 11.68.

For [9](2,4)pyridinophane derivative (**9b**): colorless powder; mp 189-190 ℃ (from EtOH); ^{13}C NMR (125.8 MHz) δ 24.6, 25.3, 25.4, 25.6, 25.7, 26.4, 26.8, 28.3, 30.0, 34.3, 36.9, 106.5, 123.0, 151.5, 152.1, 156.0, 161.6, 165.4; IR (KBr) 1700, 1656 cm^{-1}; MS (*m/z*) 315 (M^+, 71%), 231 (100). *Anal.* Calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.70; H, 8.10; N, 13.42.

For [8](2,4)pyridinophane derivative (**9c**): colorless powder; mp 194-195 ℃ (from EtOH); ^{13}C NMR (125.8 MHz) δ 23.1, 24.1, 25.5, 27.3, 27.5, 27.6, 28.3, 30.1, 34.5, 38.6, 105.7, 122.4, 151.5, 152.2, 156.4, 161.7,165.9; IR (KBr) 1700, 1658 cm^{-1}; MS (*m/z*) 301 (M^+, 60%), 133 (100). *Anal.* Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.72; H, 7.80; N, 14.02.

General synthetic procedure for [6](2,4)pyridinophane derivative (9d) and pyrido[2,3-

***d*]pyrimidine derivative (12)**. A mixture of 6-amino-2,4-dimethyluracil (**4**) (310 mg, 2 mmol) and cycloalk-2-enones (**5d,e**) (2.4 mmol) in AcOH (2 mL) was heated under reflux for the period indicated in Table 1. To the reaction mixture was added DDQ (499 mg, 2.2 mmol), and the mixture was stirred at rt overnight. After the AcOH was removed, the residue was dissolved in benzene (10 mL) containing NEt_3 (1 g, 9.9 mmol). The benzene was evaporated and the resulting residue was separated by column chromatography on Al_2O_3. The combined fractions eluted with hexane-AcOEt (4/1) gave the products (**9d**) and (**12**). The reaction conditions and the yields of the products are summarized in Table 1.

For [6](2,4)pyridinophane derivative (**9d**): colorless powder; mp 165-166 °C (from EtOH); IR (KBr) 1697, 1656 cm^{-1}; MS (*m/z*) 273 (M^+, 60%), 149 (100). *Anal.* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.87; H, 7.01; N, 15.23.

For compound (**12**): colorless prisms; mp 155-156 ℃ (from AcOEt) (lit.,[16d] mp 157-158 ℃); ^{1}H NMR (500 MHz) δ 1.63-1.76 (4H, m), 1.89 (2H, quint, *J*=5.8), 2.85 (2H, dd, *J*=6.8, 4.2), 3.08 (2H, t, *J*=5.8), 3.47 (3H, s), 3.71 (3H, s), 8.10 (1H, s); ^{13}C NMR (125.8 MHz) δ 26.3, 28.1, 28.3, 29.3, 32.3, 34.3, 39.8, 108.0, 133.7, 136.7, 148.5, 151.8, 161.8, 169.5; IR (KBr) 1711, 1672 cm^{-1}; MS (*m/z*) 259 (M^+, 100%).

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