Regulation of dynamic structure of cyclophanes by their complexation with the porphyrin

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ABSTRACT

Dithia[3.3]metacyclophanes which consist of the pyridine unit connecting to the different positions of the parent cyclophane skeleton have been prepared. Conformational change has been observed for the cyclophane having a 4-substituted pyridine unit by binding to the porphyrin. In contrast the porphyrin binding has no influence on conformational behavior of the cyclophane having a 3-substituted pyridine unit.

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Cyclophanes known as bridged aromatic compounds have been intensively investigated from various points of view because of their unique characteristics for the last few decades.[1] One of the most characteristic features of cyclophanes is their dynamic structure based on the conformational flexibility.[2] Thus, the conformational properties have been well studied in various cyclophane systems. Meanwhile we have been interested in the small-sized dithia[3.3]metacyclophane system because of their unique π systems owing to strong transannular π–electronic interactions between aromatic components in close proximity.[3] These dithia[3.3]metacyclophanes exhibit conformational features based on their ring inversion between the *syn* and *anti* conformations.[3i,4] Control of this conformational behavior is one of the attracting topics because some substantial characteristics of cyclophanes highly depend on their dynamic structures. On the other hand porphyrins are known to bind the pyridine derivatives.[5]
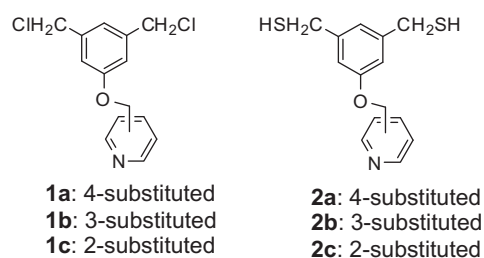
We have already reported the syntheses and properties of pyridinophanes that are the cyclophanes consisting of the pyridine component.[6] In this respect we describe here the conformational regulation of pyridinophanes by complexation with the porphyrins.

Starting with 5-hydroxyisophthalic acid, esterification and reaction with chloromethyl pyridines, followed by reduction, and chloromethylation gave the chloromethyl compounds **1a–c**. The sulfanylmethyl compounds **2a–c** were obtained from **1a–c** (see Fig. 1). The coupling reactions of **1a–c** and **2a–c** were carried out using Cs_2CO_3 as a base under a highly diluted condition to give

the corresponding pyridinophanes **3a–c** and **3e** in the yields of 43–57% (see Fig. 2).

The ^1H NMR spectral titration has been carried out for **3a–c** with the zinc porphyrin **4a**. Figure 3 shows the profile of the ^1H NMR spectrum of **3a** on addition of **4a**.

The addition of **4a** induces the upfield shifts for the protons (H_A and H_B) neighboring the nitrogen atom, indicating that the binding of porphyryin against pyridinophane should occur. In over 1:3 ratio no remarkable shifts were observed. In accordance with this porphyrin binding the upfield shift of the inner proton (H_C) is observed as shown in Figure 3. It has been well known that an extensive upfield shift of the proton at the inner position in analogous [2.2]metacyclophanes is recognized due to the strong shielding effect of the opposite aromatic ring in the *anti* conformation.[7] It has also been reported that there exists a rapid inversion between a *syn* conformation and an *anti* conformation in the dithia[3.3]metacyclophane system at room temperature.[8] The addition of **4a** to the

Figure 1. Chemical structures of **1** and **2**.

1a: 4-substituted
1b: 3-substituted
1c: 2-substituted

2a: 4-substituted
2b: 3-substituted
2c: 2-substituted

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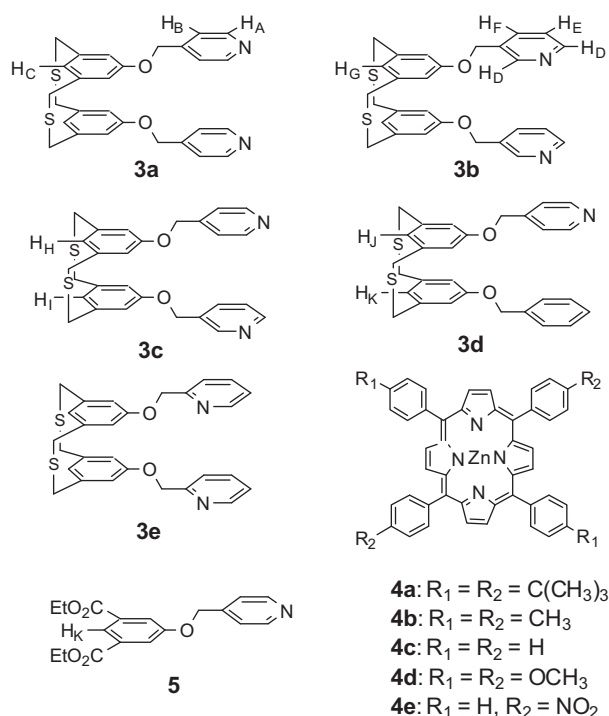
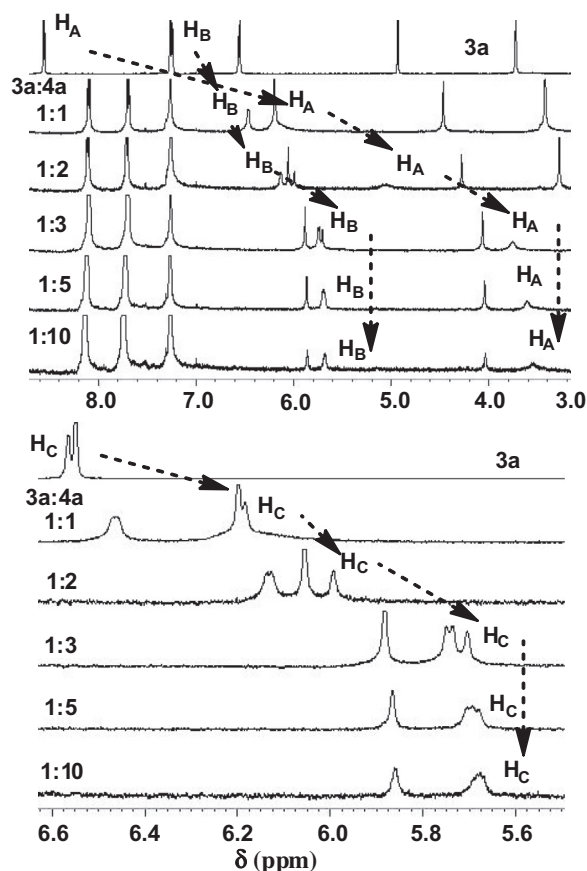**Figure 2.** Chemical structures of **3**, **4**, and **5**.

Figure 3. Partial NMR spectra of **3a** on addition of **4a**.

referential compound **5** under the same condition has little influence on the chemical shift of the inner proton (H_K) in **5**. Taking these results into account the upfield shift of the inner proton
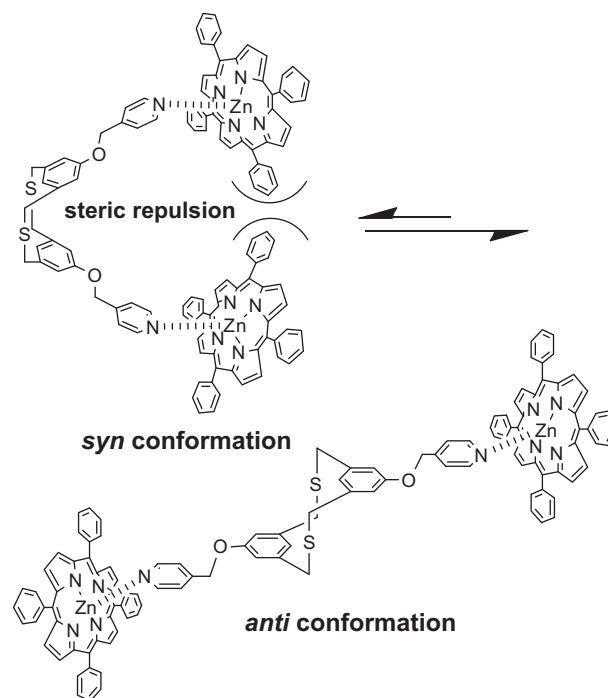

Figure 4. Preference for the *anti* conformation in the cyclophane–porphyrin system.

(H_C) seen in Figure 3 strongly suggests that the contribution of the *anti* conformation increases on the addition of porphyrin. This preference for the *anti* conformation can be considered as consequences of hindrance for formation of the *syn* conformation by means of the bulky aromatic cyclophane component binding the porphyrin ring as illustrated in Figure 4.

A similar ^{1}H NMR spectral titration was done for the pyridinophane **3b** and **4a** as shown in Figure 5.

The binding of porhyrin to **3b** can also be confirmed by the upfield shifts for the protons (H_D, H_E, and H_F) on addition of **4a**, however, the chemical shift of the inner proton (H_G) shows almost no change in contrast to **3a**. No chemical shift of the inner proton in the pyridinophane **3b** indicates that the binding of porphyrin to **3b** might have little effect on its conformational inversion, meaning that the ring inversion takes place without bumping between two bulky cyclophane components attached by the porphyrin rings. This should be due to the binding of porphyrin on the position of 3-substituted nitrogen in pyridinophane.

In order to confirm this assumption we have also examined the ^{1}H NMR spectral titration employing the pyridinophane **3c** and **3d** as shown in Figure 6. The inner protons (H_H and H_I) in **3c** exhibit about 0.45 ppm upfield shift on addition of the porphyrin **4a**. Under similar condition the upfield shifts for the inner protons (H_J and H_K) in **3d** are 0.33 ppm and 0.27 ppm, respectively. These values are smaller than the corresponding shift (0.88 ppm) recognized for **3a**, indicating that the *anti* conformation makes less contribution to the process of inversion between the *syn* and *anti* conformations compared with **3a**.

These results strongly suggest the bulky porphyrin ring on the position of 3-substituted nitrogen has a slight effect on the ring inversion in pyridinophanes. No apparent binding of **4a** against the pyridinophane **3e** was observed probably due to the steric hindrance.

Temperature should be considered for binding of porphyrin to pyridine derivatives. Thus, we have examined the conformational behavior of the porphyrin-bound pyridinophane **3a** depending on the temperature as shown in Figure 7.
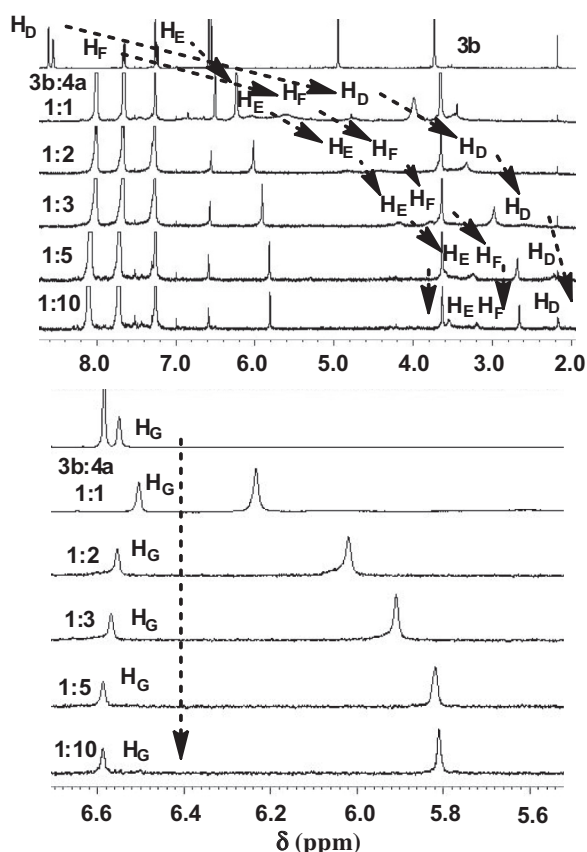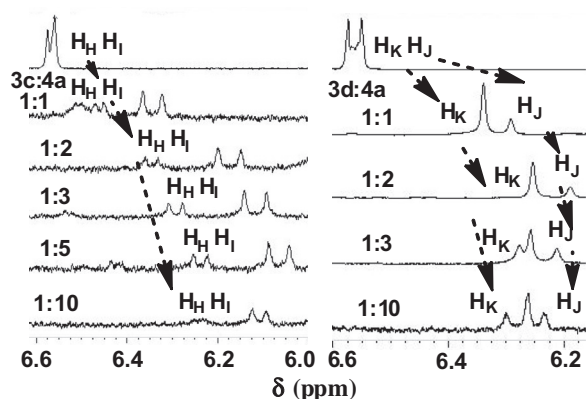
Figure 5. Partial NMR spectra of 3b on addition of 4a.

Figure 6. Partial NMR spectra of 3c and 3d on addition of 4a.

Figure 7. Partial VT spectra of 3a and 4a.

the temperature is considered to promote a dissociation of porphy-rin from the porphyrin-bound pyridinophanes. From this point of view it can be confirmed that movement to *anti* conformation in the conformational exchange of pyridinophanes is triggered by complexation of porphyrin toward pyridinophanes.

The observations obtained here imply that the binding of por-phyrin regulates the ring inversion of pyridinophanes. This binding should be dependent on the structure of porphyrins. Thus, some porphyrin derivatives (4b–e) have been prepared and the associa-tion constants in their binding against pyridinophanes have been calculated by the NMR titrations as summarized in Table 1.

The chemical shift changes of the inner protons upon addition of porphyrin are also inserted in Table 1. The association constants obtained for 3a with 4a show the same order as to those for 3a with 4b, 4c, and 4d. In these cases the chemical shift changes of the inner proton in 3a on addition of 4a, 4b, 4c, and 4d are from 0.88 to 1.23 ppm. A large association constant is observed for 3a and 4e, which can be ascribed to the nitro group on the porhyrin working as an electron-withdrawing group. This large association constant seems to be consistent with the largest upfield shift of the inner proton. This fact also supports the assumption that the binding of porphyrin should hamper the *syn* conformation, result-ing in preference for the *anti* conformation. The association con-stants of the same order of $10^7 \, M^{-2}$ for 3b with 4a–e were confirmed as for 3a. These results well agree with strong binding of porphyrin against 3b anticipated by the NMR titration. In this case the largest association constant was likewise obtained for ni-tro porphyrin 4e. Contrary to 3a no obvious chemical shifts of the

There was observed an upfield shift of the inner proton (H_C) in accordance with the shifts of the protons (H_A and H_B) as the tem-perature was going down to -30 °C. With more cooling down the corresponding peaks disappeared owing to an extensive broaden-ing. The upfield shifts of the protons (H_A and H_B) mean there is an enhancement in binding of porphyrin toward pyridinophane 3a when the temperature goes down. A preference for the *anti* con-formation indicated by the chemical shift of the inner proton (H_C) can be ascribed to an enhanced binding of porphyrin. In contrast raising the temperature the NMR profile is apparently becoming close to that of the pyridinophane 3a itself, meaning that the pro-cess of the ring inversion in the porphyrin-bound pyridinophanes is approaching the original conformational change of 3a. Increasing

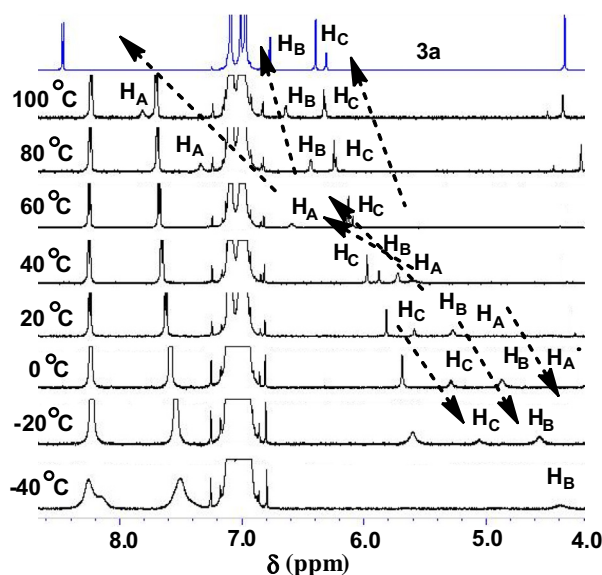Table 1
Association constants[a] and chemical shift changes[b] for 3a and 3b with 4a–4e

	Association constant (K/M^{-2})			
	3a		3b	
4a	4.0×10^7	(0.88 ppm)	4.0×10^7	(0 ppm)
4b	5.6×10^7	(0.89 ppm)	1.4×10^7	(0.02 ppm)
4c	1.3×10^7	(0.94 ppm)	1.3×10^7	(0.02 ppm)
4d	3.8×10^7	(1.23 ppm)	1.2×10^7	(0.02 ppm)
4e	1.2×10^7	(1.42 ppm)	9.4×10^7	(0.08 ppm)

[a] In chloroform, $T = 295$ K.
[b] Values are in parenthesis.

inner protons in **3b** on addition of porphyrins were recognized except for a very slight shift observed for addition of **4e**. These results strongly indicate that the binding of porphyrin at 3-substituted nitrogen in pyridinophane has nothing to do with restriction of its ring inversion.

It should be noted that conformational regulation from a *syn* conformation to an *anti* conformation in the [3.3]metacyclophane system consisting of pyridine units has been achieved by external stimuli such as addition of porhyrin. This regulation is strongly dependent on the position of substituted pyridine unit to which porphyrin binds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.116.

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