Regulation of dynamic structure of cyclophanes by their complexation with the porphyrin
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. One of the most characteristic features of cyclophanes is their dynamic structure based on the conformational flexibility. 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 p systems owing to strong transannular p–electronic interactions between aromatic components in close proximity. These dithia[3.3]metacyclophanes exhibit conformational features based on their ring inversion between the syn and anti conformations. 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.

We have already reported the syntheses and properties of pyridinophanes that are the cyclophanes consisting of the pyridine component. 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 Cs2CO3 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 (HA and HB) neighboring the nitrogen atom, indicating that the binding of porphyrin 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 (HC) 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. 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. The addition of 4a to the

![Chemical structures of 1 and 2.](attachment:fig1.png)
referential compound 5 under the same condition has little influence on the chemical shift of the inner proton (HK) in 5. Taking these results into account the upfield shift of the inner proton (HC) 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 1H NMR spectral titration was done for the pyridinophane 3b and 4a as shown in Figure 5. The binding of porphyrin to 3b can also be confirmed by the upfield shifts for the protons (HD, HE, HF) on addition of 4a, however, the chemical shift of the inner proton (HC) 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 1H NMR spectral titration employing the pyridinophane 3c and 3d as shown in Figure 6. The inner protons (HJ and HK) 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 (HJ and HK) 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.
There was observed an upfield shift of the inner proton (HC) in accordance with the shifts of the protons (HA and HB) as the temperature was going down to -30 °C. With more cooling down the corresponding peaks disappeared owing to an extensive broadening. The upfield shifts of the protons (HA and HB) mean there is an enhancement in binding of porphyrin toward pyridinophane \(3a\) when the temperature goes down. A preference for the \(anti\) conformation indicated by the chemical shift of the inner proton (HC) 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 process of the ring inversion in the porphyrin-bound pyridinophanes is approaching the original conformational change of \(3a\).

Increasing the temperature is considered to promote a dissociation of porphyrin 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 porphyrin 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 association 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 porphyrin 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, resulting in preference for the \(anti\) conformation. The association constants 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 nitro porphyrin 4e. Contrary to \(3a\) no obvious chemical shifts of the

<table>
<thead>
<tr>
<th>Compound</th>
<th>Association constant ((K/\text{M}^{-2}))</th>
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<tbody>
<tr>
<td>4a</td>
<td>(4 \times 10^7) ((0.88\text{ ppm}))</td>
</tr>
<tr>
<td>4b</td>
<td>(5.6 \times 10^7) ((0.89\text{ ppm}))</td>
</tr>
<tr>
<td>4c</td>
<td>(1.3 \times 10^7) ((0.94\text{ ppm}))</td>
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<tr>
<td>4d</td>
<td>(3.8 \times 10^7) ((1.23\text{ ppm}))</td>
</tr>
<tr>
<td>4e</td>
<td>(1.2 \times 10^7) ((1.42\text{ ppm}))</td>
</tr>
</tbody>
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\(^a\) In chloroform, \(T = 295\text{ K}\).
\(^b\) 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 porphyrin. 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.

References and notes


