Synthesis and inclusion properties of pyridinophane-linked macrocycles

Hiroyuki Takemura,*[a] Satoshi Osada,[b] Teruo Shinmyozu[c] and Takahiko Inazu[b]

[a] *Department of Chemistry, Faculty of Science, Kyushu University, Ropponmatsu 4-2-1, Chuo-ku, Fukuoka, 810 Japan*
[b] *Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki 6-10-1, Higashi-ku, Fukuoka, 812 Japan*
[c] *Institute for Fundamental Research of Organic Chemistry, Kyushu University, Hakozaki 6-10-1, Higashi-ku, Fukuoka, 812 Japan*

The macrocyclic host molecules 1 and 2 have been synthesized in satisfactory yields. These cyclophane-linked structures produce electron-rich cavities because the lone pairs of 2,11-diaza[3.3](2,6)-pyridinophane and pyridine rings converge into the cavities. Although compound 1 strongly binds guanidinium ion and urea, compound 2 showed weak complexation toward these guests. In the inclusion of guests by hydrogen bonds, the cooperation of the pyridinophane donor sites plays a very important role. Interestingly, 1 adsorbed water molecules in solution to give the hydrated compound 1·6H_2O.

Previously, we have described the properties of the cage compound **4**, whose structure consists of six pyridine rings. Since the pyridine lone pairs converge into the spherical cavity, compound **4** showed a strong affinity for cations such as protons, alkali metal ions and ammonium ions.[1] The structure of this compound is suitable for the inclusion of spherical chemical species, but not for larger organic guest species. In order to extend the inclusion ability toward organic guest species, we designed compounds **1** and **2**, whose structures also consist of pyridine rings. Compound **1** corresponds to the bond isomer of cage compound **4**: it has the same kind and number of donor atoms, but the geometry of the binding sites is quite different from that of **4**. The molecules of **1** and **2** have crown ether-like shallow cavities whose sizes are estimated to be about 6 × 5 Å and 8.4 Å in diameter, respectively. Pyridine and 2,11-diaza[3.3](2,6)pyridinophane are good ligands,[2] the inclusion ability of the latter toward cationic guest species being enhanced by the basicity of the cavity.[3] In these compounds, since 10 or 15 lone pairs of nitrogen atoms can be directed into the cavities, the inclusion of some guest species by hydrogen bonds or cation–dipole interactions is to be expected. In a previous report, the synthesis of benzene analogues of **1** and **2** was described, the former giving a 1 : 1 clathrate compound with benzene. However, these two analogues showed no inclusion phenomena in solution.[4]

In this report, a simple, simultaneous synthesis of both host molecules **1** and **2** is described, and the inclusion phenomena of guanidinium cation and urea, as well as the interesting hydration phenomenon of compound **1** are discussed.

Results and discussion

Synthesis

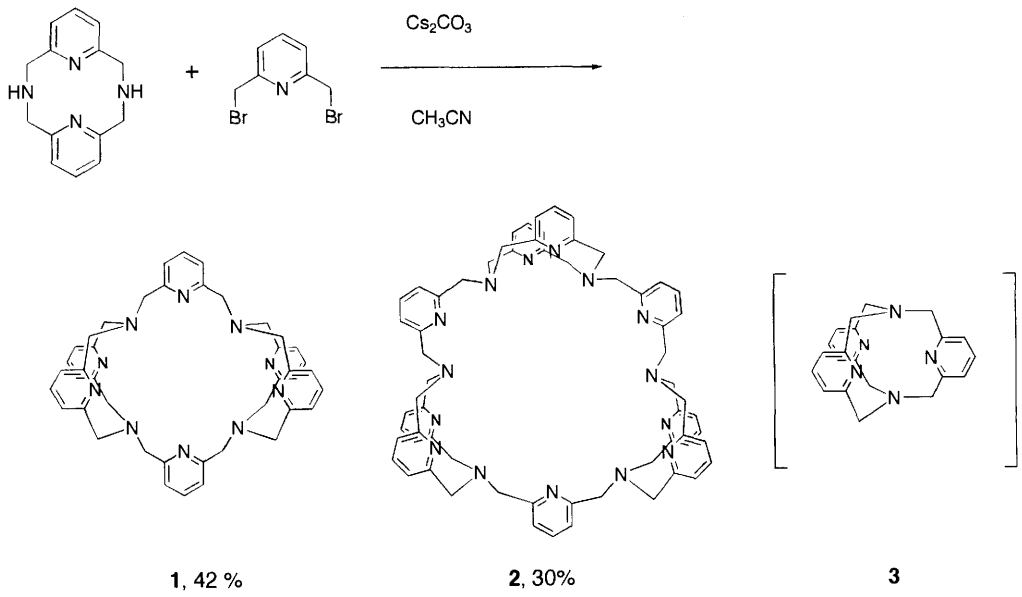
Cyclization can be achieved by a reaction between 2,11-diaza[3.3](2,6)-pyridinophane and 2,6-bis(bromomethyl)pyridine in the presence of Cs_2CO_3 as a base (Scheme 1). Without using high-dilution techniques, the macrocycles **1** and **2** were obtained in good yields (totally 72%). The monomeric bicyclic compound **3** was not generated. Lehn *et al.* attempted to synthesize compound **3** by direct coupling between 2,6-bis(aminomethyl)pyridine and 2,6-bis(bromomethyl)pyridine, but they obtained compound **1** instead.[5] However, neither the characterization nor the inclusion phenomena of **1** have been reported. We also tried to synthesize compound **3** starting from 2,11-diaza[3.3](2,6)pyridinophane using Li^+ or proton template syntheses,[6] but **3** was not detected.

Mobility of molecules 1 and 2

The mobility of the pyridinophane moiety of compound **1** strongly depends on the solvent used. In $CDCl_3$, the methylene signal of pyridinophane appears as an AB quartet (J 12 Hz) at 25 °C (Fig. 1a), but the addition of CD_3OD (1/3 of the original amount of the solution) into the $CDCl_3$ solution changed the quartet into a broad singlet. In CD_2Cl_2, the signal appeared as a relatively broad singlet. The AB quartet was also observed in [$^2H_6$]-DMSO (J 12 Hz). At present, the reason for this solvent-dependency is unclear, but one possibility is complex formation between **1** and the solvents. For example, Cl_3C–D · · · N(**1**) or O=S(CD_3)$_2$ · · · N(**1**). Here, N(**1**) shows the nitrogen atoms of **1**. The complex formation fixes the pyridinophane moiety into *syn* geometry, and therefore the methylene of the pyridinophane splits into the AB quartet. In [$^2H_6$]-DMSO at elevated temperatures (~ 100 °C), the methylene signals coalesce into a singlet which shows the *syn–anti* interconversion of the pyridinophane moiety. According to the coalescence temperatures of the methylene signal (270 MHz, 70 °C), the energy barrier ($\Delta G^{\ddagger}$) of the *syn–anti* interconversion in the solvent was estimated to be 15.8 kcal mol^{-1}. On the other hand, in the solvents mentioned above, compound **2** shows the methylene signal as a sharp singlet at room temperature which means that the *syn–anti* interconversion of the pyridinophane moiety is rapid, and that the complexation ability is weak. The energy barrier ($\Delta G^{\ddagger}$) of the interconversion was estimated to be 13.6 kcal mol^{-1} in $CDCl_3$ by means of low-temperature NMR spectra (270 MHz, T_c −23 °C).

Hydration of macrocycle 1

Interestingly, the addition of a drop of water to a solution of **1** in $CDCl_3$ broadened the methylene signals (Fig. 1b). The aromatic protons shifted to higher fields and the signals broadened, while the signal of dissolved water in the solution shifted to low fields (2.6–3.0 ppm). In general, the signal of



Scheme 1 Synthesis of macrocyclic compounds **1** and **2**

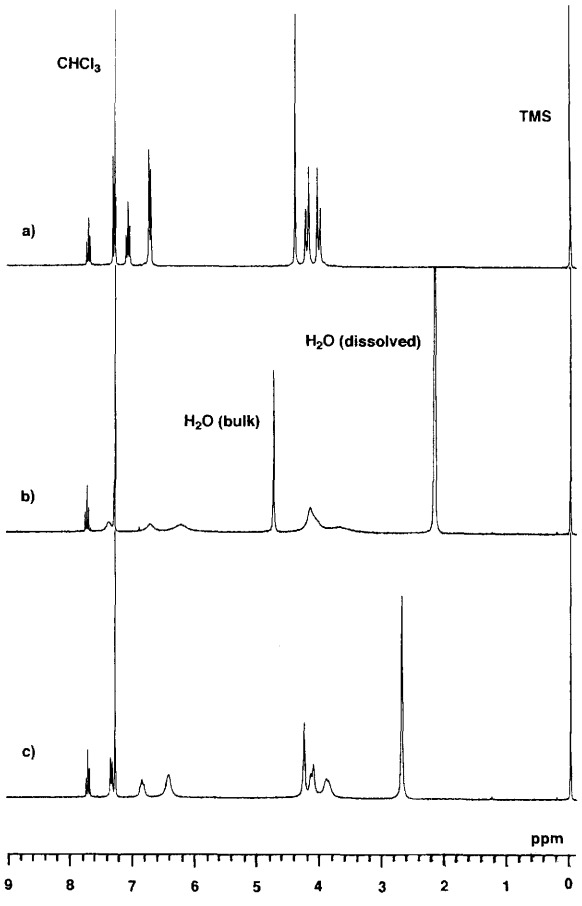


Fig. 1 ^{1}H NMR spectral changes of **1** upon addition of water in $CDCl_3$: (a) compound **1** in dry $CDCl_3$; (b) after shaking solution (a) with a drop of water; (c) after drying solution (b) with $MgSO_4$ for 24 h

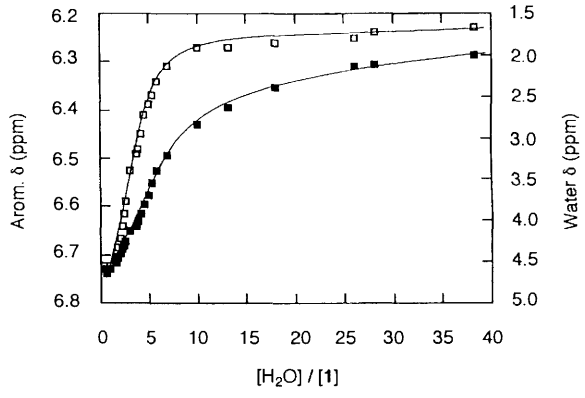


Fig. 2 Plots of chemical shifts of **1** (3-position of pyridine rings of pyridinophane moiety) and water protons *vs.* $[H_2O]/[\mathbf{1}]$: ⊟ = aromatic protons and ■ = water protons

water dissolved in $CDCl_3$ appears at 1.5 ppm. In a solution of **2**, the water signal appears at 1.8 ppm. Thus, the presence of hydrogen bonds between **1** and H_2O is apparent. Even after the solution had been dried with $MgSO_4$ for 24 h, the spectrum showed the water signal at 2.7 ppm, which corresponds to at least 8 water molecules for one molecule of **1** (Fig. 1c). The water hydrated to **1** was removed when the compound, **1**·$n$$H_2O$, was heated at 100 °C *in vacuo* (*ca.* 0.3 Torr) overnight. Alternatively, a solution of **1**·$n$$H_2O$ was heated in pyridine at 100 °C. The precipitates thus obtained appeared to be water-free **1**. Several water inclusion complexes were reported and the structures of the water molecules in the cavities were clarified by X-ray crystallographic analysis: some macrocyclic compounds complexed with water molecules,[7] and the β- and γ-cyclodextrin incorporate 7 and 12 water molecules in their cavities, respectively.[8] However, the remarkable spectral changes brought about by hydration in an aprotic solvent, as in the case of compound **1**, have not been reported yet. The main peak in the FAB mass spectra of **1**·$n$$H_2O$ was at 687 $(M + H)^+$, the signal of $(M + H_2O)$ being very small (*ca.* 4%). The OH stretching mode of **1**·$n$$H_2O$ in the IR spectrum (KBr disk) appeared around 3400 cm^{-1} but it did not prove the existence of specific strong hydrogen bonds. In order to clarify the stoichiometry of the **1**·$n$$H_2O$ complex, NMR titration experiments were carried out. The 3-position of the aromatic protons of the pyridinophane moiety shifted to higher fields as the H_2O:**1** ratio increased. The plots of the shift of the aromatic protons (δ, ppm) *vs.* H_2O:**1** show a saturation point at H_2O:**1** = 6. The chemical shift of the water protons has the same tendency (Fig. 2). The splitting pattern of the CH_2 of the pyridinophane moiety depends on the water content: it becomes a singlet at H_2O:**1** = 1.7 and then splits into the AB quartet again (Fig. 3). Also here, the solvent properties and complex formation affect the appearance of the methylene protons, as mentioned above. The association constant of the hydration

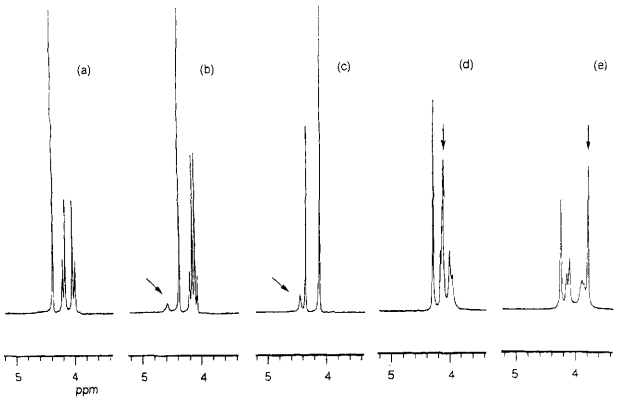


Fig. 3 The spectral change of the CH_2 signal (pyridinophane moiety) depends on the water content in the $CDCl_3$ solution. The arrows show the water signal. $[H_2O]/\mathbf{1}$ = (a) 0, (b) 0.9, (c) 1.7, (d) 4.0, (e) 5.7

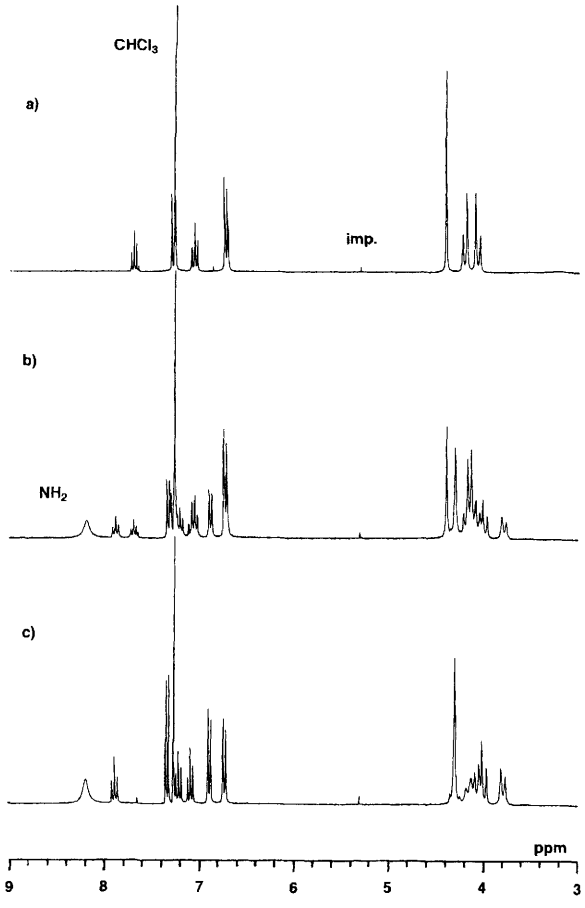


Fig. 4 ^1H NMR spectra of complex formation of **1** with guanidinium ion in $CDCl_3$: (a) free ligand; (b) after addition of solid guanidinium nitrate to the solution (10 min later); (c) 2 days after

could not be estimated because the analysis of the 1:6 equilibrium system is difficult and not reliable enough.[9] Further information on the hydrated structure of **1**·6H_2O† has not been obtained so far: it is unclear whether the water molecules are located inside the cavity as cyclodextrins, or they are hydrogen bonded from the outside of the cavity. An attempted crystallographic analysis of **1**·6H_2O was unsuccessful since a single crystal adequate for the analysis could not be obtained.

In the case of compound **2**, no hydration phenomenon was observed.

† A referee has suggested that since the stoichiometry of this structure is, at present, uncertain it is more accurately described as **1**·nH_2O (n = 5–7).

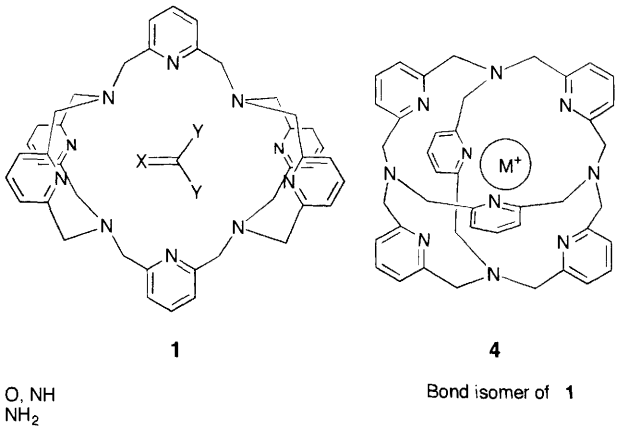


Fig. 5 Inclusion of the guest species

Inclusion phenomena with organic guests

The inclusion phenomena of **1** and **2** with two organic guests (guanidinium salt and urea) were observed under solid–liquid extraction conditions. The addition of solid guanidinium nitrate to a solution of **1** in $CDCl_3$ immediately caused a change in the spectrum. After 2 days, the changes were complete and a 1:1 complex was formed (Fig. 4). The NH_2 protons of the guanidinium ion appeared at 8.2 ppm as a broad singlet. In the absence of **1**, no NH_2 signal was observed in $CDCl_3$. Urea and **1** formed a 1:2 complex in the same solvent. The NH_2 proton of urea appeared at 5.8 ppm. The presence of hydrogen bonds between **1** and urea is apparent because the amino protons of urea in $CDCl_3$ appear at 4.4 ppm.

In view of the remarkable broadening and chemical shift of the pyridinophane signals observed, the binding sites of **1** with water, guanidinium ion and urea are clearly the pyridinophane moieties (see Figs. 1 and 4). Bell *et al.* have reported host molecules which bind guanidinium ion and urea molecules by hydrogen bonds between the host's sp^2 nitrogen atoms and the guest's amino groups.[10] 2,4,6-Triaminopyrimidine, although having some of the structural elements present in guanidine and urea, failed to form an inclusion complex with **1**, probably because of its bulk and also because the host–guest hydrogen bonds are weak, its the amino protons being much less acidic than those of urea and of the guanidinium salt (Fig. 5).

Compound **2** formed a 1:1 complex with urea for which the ^1H NMR signals of the amino protons appear at 4.8 ppm. The methylene signal broadened and was slightly shifted to lower fields (~0.06 ppm). Thus, not only were the hydrogen bonds and the complexation weak, but also the equilibrium in the $CDCl_3$ solution is rapid in comparison with the **1**·urea complex. The same tendency was observed between guanidinium nitrate and **2**. The NH_2 protons of the guanidinium ion appeared at 8.7 ppm. The observed ratio of **2** to guanidinium was 3:1 but since, in this case, there was a white precipitate, the ratio is uncertain. Although the shape and size of benzene-1,3,5-triol and 2,4,6-triaminopyrimidine appear ideal to fit into the cavity of **2** and were, therefore, expected to form hydrogen bonded inclusion complexes, they failed to do so in $CDCl_3$ or [$^2H_6$]-DMSO. In the case of **1**, the cooperation of the two pyridinophanes strongly assists the complexations: the pyridinophane binding sites are close to each other in contrast with **2** and the pyridinophane moiety is fixed in a *syn* conformation. Thus, all of the lone pairs converge into the cavity. On the other hand, the pyridinophane moiety of **2** is flexible, and the easy *syn–anti* interconversion loses the pre-organized structure. Therefore, compound **2** shows weaker complexation ability than compound **1**. These results should be helpful to the further design of pyridinophane-based

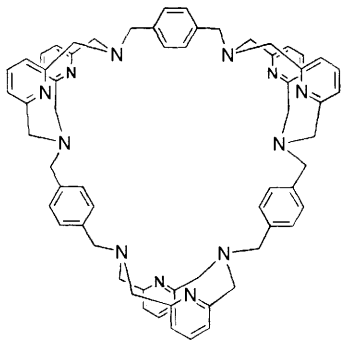


Fig. 6 Structure of compound **5**

macrocyclic compounds, which show strong and selective inclusion abilities.‡

Experimental

General

All mps were measured in Ar sealed tubes and were uncorrected. The ^{1}H NMR spectra were recorded on a JEOL-GSX270 (270 MHz) NMR spectrometer. The FAB mass spectra were recorded on a JEOL JMS-SX/SX102A, tandem mass spectrometer.

Synthesis of macrocycles 1 and 2

A solution of 2,11-diaza[3.3](2,6)pyridinophane (70 mg, 0.29 mmol),[4c,11] Cs_2CO_3 (650 mg, 2.0 mmol) in acetonitrile (150 cm^3) containing water (20 cm^3) was stirred and heated under reflux. After 1 h, a solution of 2,6-bis(bromomethyl)pyridine (79 mg, 0.30 mmol) in acetonitrile (50 cm^3) was added over a period of 30 min and the mixture was heated for 3 days.§ The solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 solution was repeatedly washed with water and evaporated. The resultant powder was recrystallized from CH_2Cl_2–MeCN. Compound **2** was precipitated at first as cotton-like white fine crystals (29.8 mg, 30%). Later, concentration of the mother liquor afforded compound **1** as white crystals (42.3 mg, 42%). *Compound* **1**: mp 294 °C; an analytical sample was recrystallized from CH_2Cl_2–C_6H_6 [Found: C, 72.6; H, 6.1; N, 19.45. $C_{42}H_{42}N_{10}$·1/6 (CH_2Cl_2·C_6H_6) requires C, 72.61; H, 6.12; N, 19.62%]. The quantities of solvents included in the analytical sample were confirmed by means of the ^{1}H NMR spectrum; δ_H(270 MHz; $CDCl_3$; Me_4Si) 7.72, 7.70, 7.67 (2 H, d, *J* 8, ArH), 7.30, 7.27 (4 H, d, *J* 8, ArH), 7.09, 7.06, 7.03 (4 H, t, *J* 8, ArH), 6.72, 6.70 (8 H, d, *J* 8, ArH), 4.40 (8 H, s, CH_2), 4.20, 4.02 (16 H, ABq, *J* 12, CH_2); *m/z* (FAB) 687 (M + H^+, 100%). *Compound* **2**: mp > 346 °C (decomp.); an analytical sample was recrystallized from CH_2Cl_2–C_6H_6 [Found: C, 72.7; H, 6.2; N, 19.6. $C_{63}H_{63}N_{15}$·1/4 (CH_2Cl_2·C_6H_6) requires C, 72.61; H, 6.12; N, 19.62%]. The quantities of solvents included in the analytical sample were confirmed by means of the ^{1}H NMR spectrum; δ_H(270 MHz; $CDCl_3$) 7.81, 7.78, 7.75 (3 H, t, *J* 8, ArH), 7.53, 7.50 (6 H, d, *J* 8, ArH), 6.88, 6.85, 6.82 (6 H, t, *J* 8, ArH), 6.64, 6.61 (12 H, d, *J* 8, ArH), 4.14 (s, 12 H, CH_2), 3.92 (s, 24 H, CH_2); *m/z* (FAB) 1030 (M + H^+, 100%).

Synthesis of compound 5

This compound was synthesized in a manner similar to that for compounds **1** and **2**, mp > 347 °C (decomp.); an analytical sample was recrystallized from CH_2Cl_2–MeCN (Found: C, 74.9; H, 6.5; N, 15.7. $C_{66}H_{66}N_{12}$·½CH_2Cl_2 requires C, 74.66; H, 6.31; N, 15.71%). The amounts of solvents included in the analytical sample were determined by means of the NMR spectrum; δ_H(270 MHz; $CDCl_3$; Me_4Si) 7.56 (2 H, s, ArH), 6.96, 6.93, 6.90 (6 H, t, *J* 8, ArH), 6.61, 6.59 (12 H, d, *J* 8, ArH), 3.92 (12 H, s, benzene-CH_2), 3.79 (s, 24 H, Py·CH_2); *m/z* (FAB) 1027 (M + H^+, 100%).

‡ The synthesis of the *p*-xylylene-bridged macrocyclic compound was also attempted but only a trimeric compound **5** was obtained (19%) even under high-dilution conditions (Fig.6). This compound did not show the inclusion phenomena described above: the substitution of the pyridine rings of **2** with *p*-xylylene units remarkably decreased the complexation ability.

§ In < 24 h, the reaction yielded considerable amounts of acyclic products.

Acknowledgements

We thank Miss Mie Tomonou of the Faculty of Science, Kyushu University for the FAB mass spectral measurements.

References

1 H. Takemura, T. Shinmyozu and T. Inazu, *J. Am. Chem. Soc.*, 1991, **113**, 1323.

2 (*a*) F. R. Fronczek, A. Mamo and S. Pappalardo, *Inorg. Chem.*, 1989, **28**, 1419; (*b*) J.-M. Lehn, *Pure Appl. Chem.*, 1980, **52**, 2441; (*c*) S. Muralidharan, M. Hojjatie, M. Firestone and H. Freiser, *J. Org. Chem.*, 1989, **54**, 393; (*d*) T. W. Bell and F. Guzzo, *J. Chem. Soc., Chem. Commun.*, 1986, 769; (*e*) J. C. R. Ubis, B. Alpha, D. Plancherel and J.-M. Lehn, *Helv. Chim. Acta*, 1984, **67**, 2264; (*f*) W. D. Kim, G. E. Kiefer, F. Maton, K. McMillan, R. N. Muller and A. D. Sherry, *Inorg. Chem.*, 1995, **34**, 2233; (*g*) H.-D. Krüger, *Chem. Ber.*, 1995, **128**, 531; (*h*) W. D. Kim, D. C. Hrncir, G. E. Kiefer and A. D. Sherry, *Inorg. Chem.*, 1995, **34**, 2225.

3 (*a*) J. S. Bradshaw, G. E. Maas, J. D. Lamb, R. M. Izatt and J. J. Christensen, *J. Am. Chem. Soc.*, 1980, **102**, 467; (*b*) F. Vögtle, U. U. Körsgen, H. Puff and H. Reuter, *Chem. Ber.*, 1989, **122**, 343.

4 (*a*) H. Takemura, T. Shinmyozu and T. Inazu, *Tetrahedron Lett.*, 1988, **29**, 1789; (*b*) H. Takemura, T. Hirakawa, T. Shinmyozu and T. Inazu, *Tetrahedron Lett.*, 1984, **25**, 5053; (*c*) H. Takemura, M. Suenaga, K. Sakai, H. Kawachi, T. Shinmyozu, Y. Miyahara and T. Inazu, *J. Inclusion Phenom.*, 1984, **2**, 207.

5 B. Alpha, E. Anklam, R. Deschenaux, J.-M. Lehn and M. Pietraskiewicz, *Helv. Chim. Acta*, 1988, **71**, 1042.

6 P. L. Anelli, F. Montanari and S. Quici, *J. Org. Chem.*, 1985, **50**, 3453.

7 (*a*) T. L. Tarnowski and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1976, 661; (*b*) R. C. Helgeson, T. L. Tarnowski and D. J. Cram, *J. Org. Chem.*, 1979, **44**, 2538; (*c*) I. Goldberg, *Acta Crystallogr., Sect. B*, 1978, **34**, 3387; (*d*) D. Mootz, A. Albert, S. Schaefgen and D. Stäben, *J. Am. Chem. Soc.*, 1994, **116**, 12045; (*e*) L. Mèndez, R. Singleton, A. M. Z. Slawin, J. F. Stoddart, D. J. Williams and M. K. Williams, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 478; (*f*) R. P. Bonar-Law and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1995, **117**, 259; (*g*) C. M. Pearce and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1119.

8 (*a*) K. Lindner and W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 694; (*b*) J. M. Maclennan and J. J. Stezowski, *Biochem. Biophys. Res. Commun.*, 1980, **92**, 926.

9 K. A. Connors, *Binding Constants-The Measurement of Molecular Complex Stability*, John Wiley & Sons, New York, 1987, p. 189.

10 (*a*) T. W. Bell and J. Liu, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 923; (*b*) T. W. Bell and J. Liu, *J. Am. Chem. Soc.*, 1988, **110**, 3673.

11 F. Bottino, M. D. Grazia, P. Finocchiaro, F. R. Fronczek, A. Mamo and S. Pappalardo, *J. Org. Chem.*, 1988, **53**, 3521.

Paper 5/04225I
Received 30*th June* 1995
Accepted 15*th August* 1995