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Macrocycles with two exclusive hydrogen-bonding modes

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Abstract—A series of large, 44-membered macrocycles **7a**–**e** were synthesized and characterized, which display two different diagonal binding modes. The unsubstituted macrocycle **7a** strongly binds naphthalene-2,6-dicarboxylate through hydrogen bonds with the association constant ($K_a \pm 15\%$) of 4500 M^{-1} in 40% (v/v) $CD_3CN/CDCl_3$ at 23 ± 1 °C. Introduction of an electron-withdrawing substituent (Cl) at all four corners increases the binding affinity (22,000 M^{-1} for **7b**), while that of an electron-donating substituent (pyrrolidinyl) greatly decreases it (150 M^{-1} for **7c**). The same propensity has been observed with macrocycles **7d** and **7e** bearing different substituents at two diagonal corners, suggesting that the relative population of the binding modes would be modulated by controlling the electron density of the aromatic ring.

A large number of interlocked supermolecules such as pseudorotaxanes and rotaxanes have been prepared in the last decade to develop molecular-level machines, switches and motors, etc.[1] The supermolecules have two or more distinct modes of complexation between a macrocycle and a threading molecule, and their relative population can be reversibly controlled by an external stimulation. Most of the examples were derived from the threading component bearing two different binding sites for the macrocycle, allowing for co-conformation switching based on the shuttling motion of the macrocycle. However, only limited examples of the rotaxanes derived from the macrocycle with two different binding sites have been reported to date possibly due to the synthetic difficulty of such a macrocycle, and a representative example was described by Sauvage and co-workers.[2] Herein we report the synthesis and binding properties of macrocycles **7a**–**e** with two different binding modes when dicarboxylate **8** is diagonally placed inside the cavity via hydrogen bonds. The relative population of two binding modes can be controlled by varying the substituents at the corners, implying that the system can be potentially applicable to the development of (pseudo) rotaxane-based molecular machines (Fig. 1).

For the synthesis of macrocycles **7a**–**e**, pyridine-2,6-dicarboxamide was selected as a building block due to its conformational rigidity resulting from internal

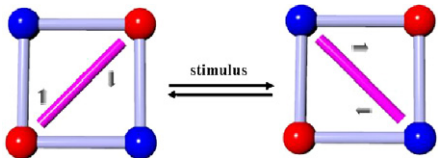

Figure 1. Schematic representation of a possible molecular machine working by rotational movement.

N(pyridine)···HN(amide) hydrogen bonds.[3] This is a crucial feature for the efficient synthesis of large macrocycles, otherwise extremely challenging due to polymerization. Macrocycles **7a**–**e** were prepared in a stepwise manner as outlined in Scheme 1. Pyridine-2,6-dicarbonyl dichloride (X = H or Cl) was coupled with a BOC-protected amine **2** to yield compound **3** (92–97%). The selective de-protection of one of the BOC groups was carried out as follows: Compound **3** was dissolved in 10% (v/v) $CF_3CO_2H/CHCl_3$ (approximately 0.02 M) in an iced water bath (0–5 °C), and the reaction was quenched with 1 N aqueous NaOH solution when the corresponding diamine was detected on thin layer chromatography (TLC) usually in 1–2 h. After the resulting mixture was purified, this process was repeated twice more with the recovered **3**, which gave the desired product in total yields of 69–89%. Coupling of **4** (2 equiv) with dichloride **1** (Y = H, or Cl, 85–96% yields), followed by de-protection (1:1 v/v $CF_3CO_2H/CHCl_3$, 90–93% yields), gave diamine **6**, which was in turn reacted with a dichloride **1** (X = H, or Cl) using a syringe pump method to give macrocycles **7a**, **7b** and

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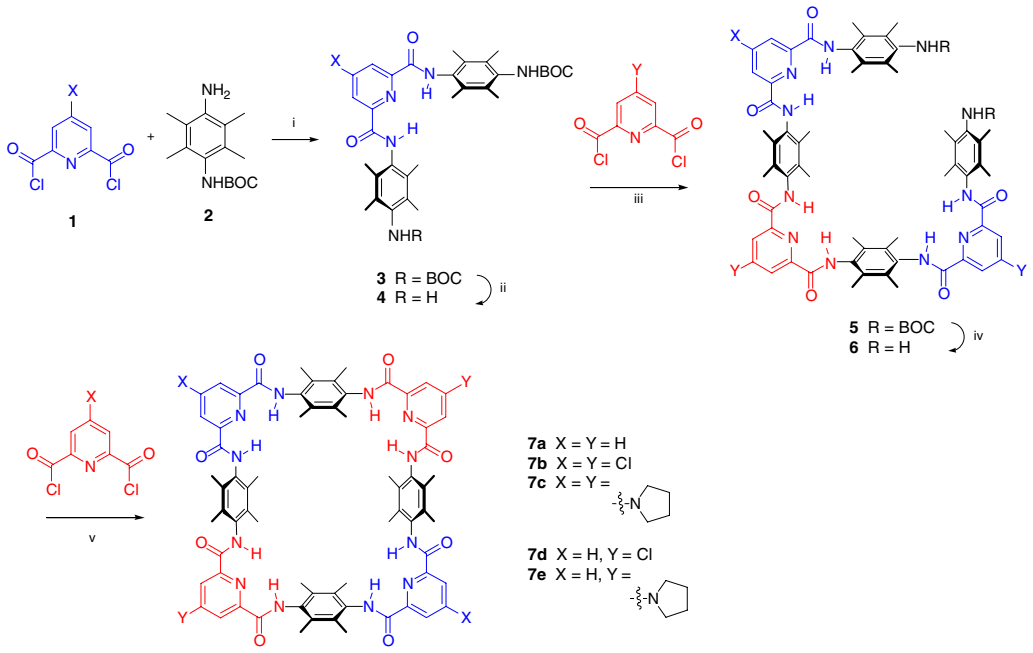
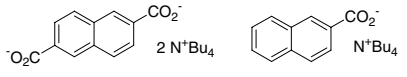


Scheme 1. Reagents and conditions: (i) NEt_3, $CHCl_3$, 0 °C to room temperature, 30 min, 92–97%; (ii) 10% (v/v) $CF_3CO_2H/CHCl_3$, 0–5 °C, 1–2 h, 69–89%; (iii) NEt_3, $CHCl_3$, 0 °C to room temperature, 30 min, 85–96%; (iv) 1:1 v/v $CF_3CO_2H/CHCl_3$, 90–93%; (v) NEt_3, $CHCl_3$, room temperature, 13 h, 42–83%.

7d. The yields of this final step are in the range of 42–83%, which is surprisingly high when considering the cyclization of the 44-membered rings.[4] This result is attributed in part to the conformational restriction by internal hydrogen bonds in the pyridine-2,6-dicarboxamide unit as mentioned above. Finally, pyrrolidine-substituted ones **7c** (76%) and **7e** (72%) were prepared by simply refluxing the corresponding chloro-substituted ones **7b** and **7d** in pyrrolidine.[5]

An energy-minimized structure of **7a** indicates that all of the amide hydrogens are directed inside the cavity with the diagonal distance of approximately 12 Å.[6] Bis(tetrabutylammonium) naphthalene-2,6-dicarboxylate (**8**) was selected as a guest, which has a complementary distance between the two carboxylate groups. In addition, **8** is a rigid molecule without any bendable bond so that two carboxylates are oriented in an opposite direction, thus enabling to simultaneously form hydrogen bonds with two diagonal corner NHs of **7a**.



8 **9**

The titration experiments were carried out in 40% (v/v) $CD_3CN/CDCl_3$ at 24 ± 1 °C, with macrocycles **7a**, **7b** and **7c** that have identical substituents at all four corners. When **8** was added, the ^1H NMR signals for the amide NHs of the macrocycles were characteristically downfield shifted owing to the hydrogen bond formation. For example, the NH signals of **7a** were shifted from 9.75 to 10.47 ppm when the concentration of guest **8** gradually increased. The non-linear squares fitting of the titration curve[7] gave the association constant (K_a ± 20%) of 4500 M^{-1}. A 1:1 complexation between **7a** and **8** was confirmed by the continuous variation method (Fig. 2c, inset).[8] For a comparison, the association constant of mono-carboxylate **9** with **7a** was determined to be 640 M^{-1} under identical titration conditions. This result clearly suggests that the NHs at two diagonal corners of **7a** are simultaneously involved in hydrogen bonds with **8** as shown in Figure 2 (top).

The substituent effects can be clearly seen in the binding studies with macrocycles **7b** and **7c**. As shown in Table 1, an electron-withdrawing group (Cl) at the pyridyl corners of **7b** increases the binding affinity (K_a 22,000 M^{-1}), while an electron-donating group (pyrrolidinyl) of **7c** greatly decreases it (K_a 150 M^{-1}). This phenomenon can be explained with repulsive interactions between the pyridyl nitrogen and the incoming carboxylate as suggested previously.[9] The electron-withdrawing group at the 4-position of the pyridyl corner reduces the electron density on the nitrogen, thus decreasing the repulsion forces and in turn the binding affinity. The electron-donating group leads to an exactly opposite consequence.

Finally, the binding properties of **7d** and **7 e** were investigated, showing two unequal binding modes resulted from different substituents at the diagonal corners (H vs Cl for **7d**, and H vs pyrrolidinyl for **7e**). The macrocycles **7d** and **7e** showed two well resolved NH signals for the unsubstituted (H) and substituted (Cl or pyrrolidinyl) sides. Moreover, degrees of the complexation-induced chemical shifts (CIS) of two NH signals are clearly different when guest **8** was added. For example, the NH signal at the chloro-substituted corners of **7d**

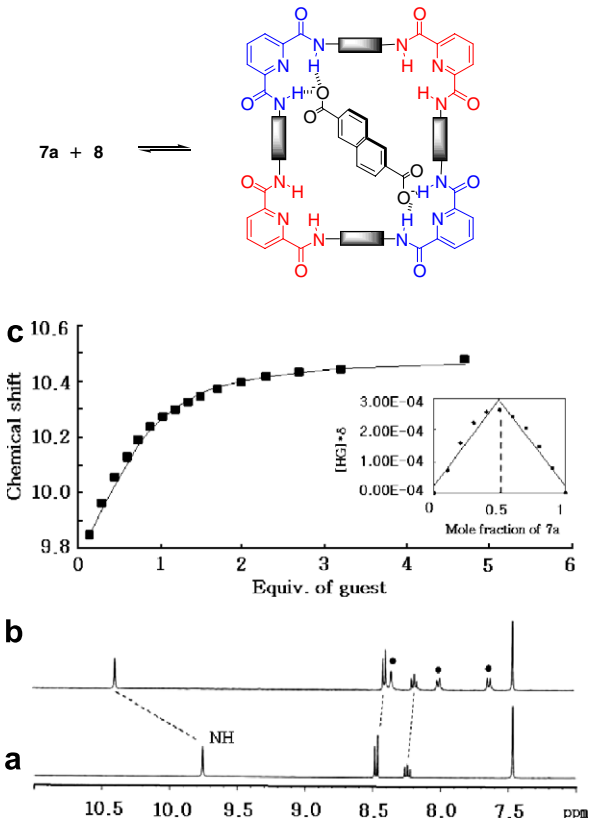


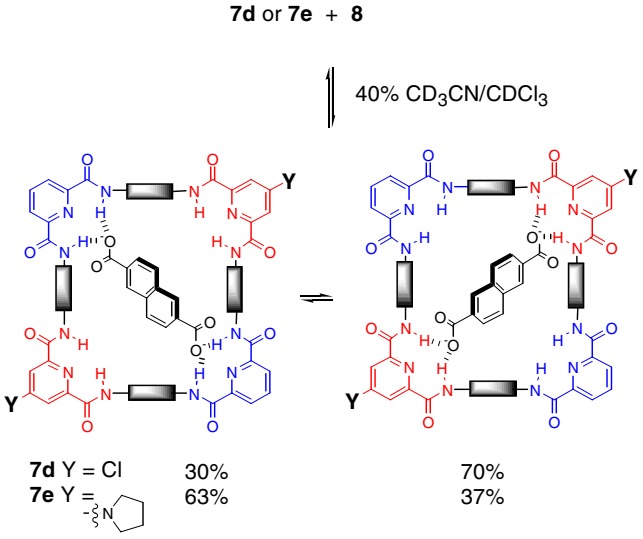
Figure 2. Partial ^{1}H NMR spectra (500 MHz, 40% $CD_3CN/CDCl_3$) of (a) **7a** (1 mM) and (b) **7a** (1 mM) + **8** (2 mM); here the signals marked with filled circles are for aromatic hydrogens of guest **8**, (c) ^{1}H NMR titration curve and a Job plot (inset) between **7a** (1 mM) and **8** in 40% $CD_3CN/CDCl_3$ at 24 ± 1 °C.

Table 1. Association constants (K_a ± 20%, M^{-1}) of **7a**–**c** and guests, **8** and **9**, in 40% $CD_3CN/CDCl_3$ at 24 ± 1 °C[a]

Host	Guest	K_a (M^{-1})	δ_{free} (NH, ppm)	δ_{comp} (calcd) (NH, ppm)
7a	**8**	4500	9.75	10.57
7a	**9**	640	9.75	10.30
7b	**8**	22,000	9.71	10.72
7c	**8**	150	9.79	10.28

[a] The ^{1}H NMR titration experiments were all duplicated and initial concentration of macrocycles and guests were 0.8–1 and 5–30 mM, respectively.

shifted from 9.71 to 10.74 ppm, while that at the unsubstituted (H) corners shifted from 9.75 to 10.23 ppm upon addition of **8** (1 equiv, ~0.8 mM in a 40% $CD_3CN/CDCl_3$) when added at room temperature. Relative population of each binding mode can be estimated based on the CIS values and the chemical shifts of the free and its complex (Scheme 2).[10] As expected, the electron-withdrawing group (Cl) increases the population up to 70%, but the electron-donating group (pyrrolidinyl) decreases it (37%) relative to the unsubstituted side, implying that the relative population of the binding modes would be modulated by controlling the electron density of the aromatic ring. More practical methods including an electrical or electrochemical redox chemistry would be employed to modulate the electron density for future application to (pseudo)rotaxane-based molecular-level machines.



Scheme 2. Relative populations of two different binding modes of complexes between macrocycles **7d** and **7e**, and dicarboxylate **8** in a 40% $CD_3CN/CDCl_3$ at 24 ± 1 °C.

In conclusion, with macrocycles displaying two different binding modes, it has been nicely demonstrated that the relative distribution of each mode can be tuned by modulating the electron density of the pyridyl ring by introducing different substituents. The modification of this system is underway to develop a rotaxane-based molecular machine.

Acknowledgements

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4. Representative procedure for the synthesis of macrocycle **7a**: A solution of the 2,6-pyridine dicarbonyl dichloride

(1.16 g, 1.1 mmol) in dry $CHCl_3$ (25 mL) and a solution of **6** (0.22 g, 1.1 mmol) and NEt_3 (0.3 mL, 2.2 mmol) in dry $CHCl_3$ (25 mL) were prepared separately. Two solutions were simultaneously added via a motor driven syringe pump to a flask containing only dry $CHCl_3$ (800 mL) over 9 h. The reaction mixture was then stirred for additional 2–3 h. The solvent was removed under reduced pressure. The solution was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was sequentially washed with minimum amount of $CHCl_3$, MeOH and diethyl ether to give **7a** (0.8 g, 82%) as a white solid. Physical and spectroscopic properties. Compound **7a**: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.12 (s, 8H, NH), 8.58 (d, 8H, $J = 7.6$ Hz), 8.22 (t, 4H, $J = 7.6$ Hz), 2.28 (s, 48H); MALD-TOF (m/z) $[MH]^+$ calcd for $C_{68}H_{69}N_{12}O_8$ 1181.54; found 1181.68.

Compound **7b**: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.03 (s, 8H, NH), 8.56 (s, 8H), 2.26 (s, 48H); MALD-TOF (m/z) $[MH]^+$ calcd for $C_{68}H_{65}Cl_4N_{12}O_8$ 1319.38 (three as ^{35}Cl and one as ^{37}Cl); found 1319.52.

Compound **7c**: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.28 (s, 8H, NH), 7.57 (s, 8H), 3.52 (m, 16H), 2.25 (s, 48H), 2.10 (m, 16H); MALD-TOF (m/z) $[MH]^+$ calcd for $C_{84}H_{97}N_{16}O_8$ 1457.77; found 1457.95.

Compound **7d**: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.13 (s, 2H, NH), 9.05 (s, 2H, NH), 8.59 (s, 4H), 8.57 (s, 4H), 8.56 (s, 8H), 8.23 (t, 2H, $J = 7.8$), 2.27 (s, 24H), 2.26 (s, 24H); MALD-TOF (m/z) $[MH]^+$ calcd for $C_{68}H_{67}Cl_2N_{12}O_8$ 1249.46; found 1249.60.

Compound **7e**: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.29 (s, 4H, NH), 9.11 (s, 4H, NH), 8.57 (d, 4H, $J = 8$ Hz), 8.21 (t, 2H, $J = 8$ Hz), 7.58 (s, 4H), 3.52 (m, 8H), 2.27 (s, 48H), 2.11 (m, 8H); MALD-TOF (m/z) $[MH]^+$ calcd for $C_{76}H_{83}N_{14}O_8$ 1319.65; found 1319.80.

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10. The relative population of each binding mode was calculated as follows. Let us assume two complexes **C1** and **C2** between **7d** (**7e**) and **8**.

$$\text{Percentage of } \mathbf{C1} = \{[\mathbf{C1}]/([\mathbf{C1}] + [\mathbf{C2}])\} \times 100$$
$$[\mathbf{C1}] = [H]_0 \times \{(\delta 1 - \delta 1_{\text{free}})/(\delta 1_{\text{comp}} - \delta 1_{\text{free}})\} = \Delta\delta 1/\Delta\delta 1_{\max}$$
$$[\mathbf{C2}] = [H]_0 \times \{(\delta 2 - \delta 2_{\text{free}})/(\delta 2_{\text{comp}} - \delta 2_{\text{free}})\} = \Delta\delta 2/\Delta\delta 2_{\max}$$

Here, $[H]_0$ is the initial concentration of a macrocycle (**7d** or **7e**), and $\delta 1$ and $\delta 2$ are observed NH chemical shifts for the substituted and unsubstituted sites, respectively, when **8** was added. $\Delta\delta 1_{\max}$ and $\Delta\delta 2_{\max}$ were deduced from the $\Delta\delta_{\max}$values obtained with **7a**, **7b** and **7c** in Table 1. Compounds **7a**, **7b** and **7c** have four identical pyridinedicarboxamide units, only two of them being hydrogen-bonded upon complexation. Consequently, in the calculation of [**C1**] and [**C2**], $\Delta\delta 1_{\max}$ and $\Delta\delta 2_{\max}$ were assumed equal to $2\Delta\delta_{\max}$. Errors in the relative population are within 2%, regardless of the amount of added guest **8**.