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Bis-Urea Macrocycles with a Deep Cavity

Guobao Huang,[a,b,‡] Zhenfeng He,[b,d,‡] Chen-Xi Cai,[b] Fangfang Pan,[c] Dingqiao Yang,*[a] Kari Rissanen,[c] and Wei Jiang*[b]

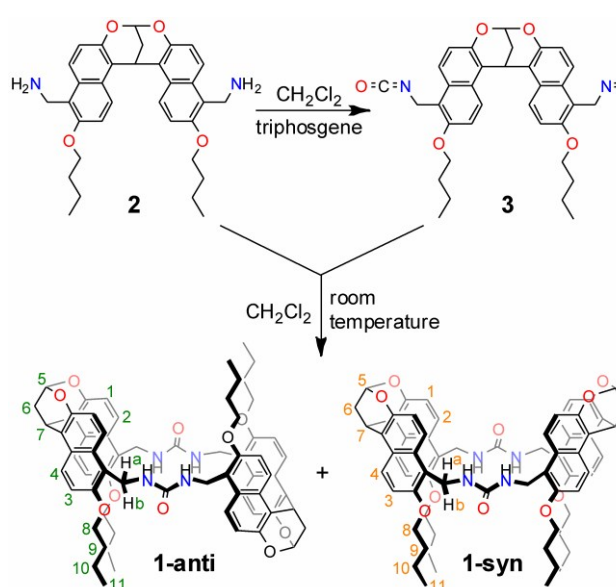**Two configurational isomers of bis-urea macrocycles have been synthesized, and their neutral molecule recognition was studied by X-ray crystallography and ¹H NMR experiments. Cooperative action between the deep cavity and the urea groups and the influence of dipole alignments on molecular recognition are discussed.**

Molecular recognition in Nature is always a source of inspiration for supramolecular chemists.[1] In enzyme binding pockets, convergent functional groups are perfectly arranged to complement the binding sites of the substrates. The cavity and the convergent functional groups work together to afford very efficient binding. Achieving enzyme-like binding is always one of the dreams of supramolecular chemists. However, in synthetic molecular receptors, functional groups are rarely incorporated into deep cavities[2], although they are often attached to the periphery of the cavities.

Selective recognition of neutral molecules in non-polar solvents is generally more difficult than ions,[3] since non-covalent interactions are usually weaker in non-charged systems. Urea macrocycles have been reported to efficiently recognize anions,[4] and self-assemble into nanotubular reaction chambers in the solid state.[5] To the best of our knowledge, urea group has not been incorporated into a deep macrocyclic cavity for the recognition of neutral molecules. Herein, we report two bis-urea macrocycles with a deep cavity. Their configurational isomerism and neutral molecule recognition have been studied.

a. School of Chemistry and Environment, South China Normal University, Guangzhou, 510006, P. R. China. E-mail: yangdq@scnu.edu.cn.
b. Department of Chemistry, South University of Science and Technology of China, No. 1088 Xueyuan Blvd, Nanshan District, Shenzhen, 518055, P. R. China. Tel: +86-755-88018316; E-mail: jiangw@sustc.edu.cn.
c. Department of Chemistry, Nanoscience Center, P. O. Box 35, FI-40014, University of Jyväskylä, Jyväskylä, Finland.
d. School of Chemical Engineering and Environment, North University of China, No. 3 Xueyuan Road, Taiyuan, Shanxi, 030051, P. R. China

‡ These authors contributed equally.
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Scheme 1 Synthetic procedure for the bis-urea macrocycles **1-anti** and **1-syn**. Numbering on the structures corresponds to the assignment of NMR signals.

Recently, we have reported dynamic imine macrocycles[6] and molecular tweezers[7] based on a bis-naphthalene cleft.[8] This cleft provides a perfect curvature for the construction of macrocycles.[9] In the present work, we designed bis-urea macrocycles **1** by combining urea groups with this bis-naphthalene cleft. Methylenes are deliberately used as linkers between the urea groups and the clefts. Thus, the NH protons of the urea groups are forced to direct inward into the cavity, providing the possibility to form hydrogen bonds with guests inside the cavity. In addition, the bis-naphthalene cleft is very electron-rich, and the macrocycles can take up guests through weak C-H···π interactions or π···π stacking.

The synthesis of the macrocycles is straightforward. The two clefts are linked together by two urea groups. Obviously, the urea formation between primary amine and isocyanate can be used to synthesize the macrocycles (Scheme 1). The diamine 2 was first converted to the isocyanate **3** by reacting it with

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Fig. 1 Partial ^{1}H NMR spectra (400 MHz, CDCl$_3$, 25 ^{o}C) of two isomers of bis-urea macrocycle **1**: (a) the one with low polarity (**1-anti**); (b) the one with high polarity (**1-syn**).

Fig. 2 X-ray single crystal structures of (a) **1-anti** and (b) **1-syn** obtained from their solution in the mixture of MeCN and CH$_2$Cl$_2$. The solvents outside of the cavity are removed for clarity. The MeCN molecules are disordered in the cavity of **1-syn** due to the symmetry. (c) chemical structures of neutral guests **4 − 8**. Numbering on the structures corresponds to the assignment of NMR signals.
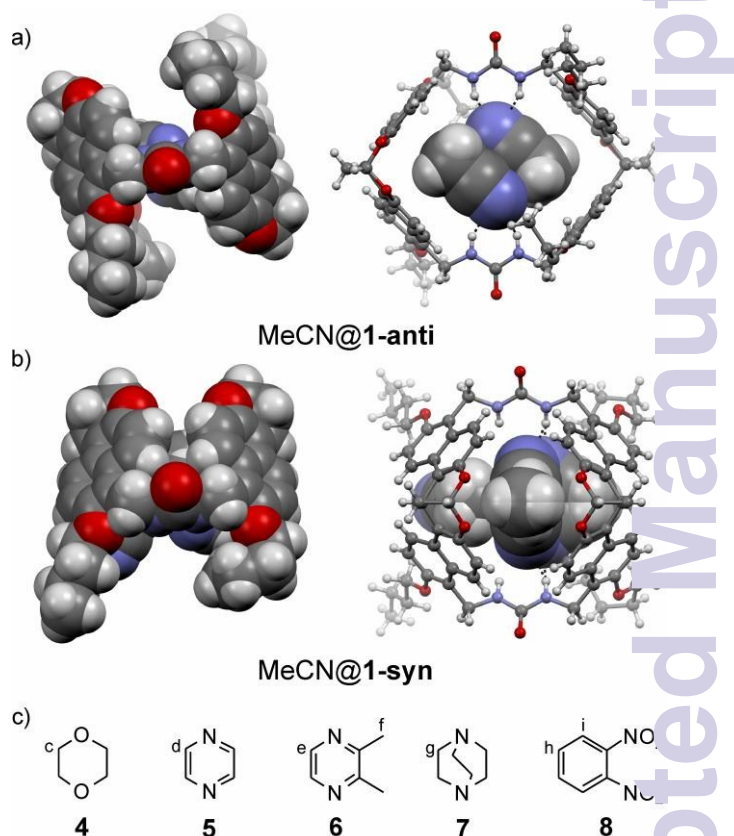
triphosgene at room temperature. Then, compounds **2** and **3** were reacted at room temperature under pseudo-high dilution condition to afford the urea macrocycles **1**. The isolated total yield of the [1+1] macrocyclization product is decent (52%).

Theoretically, two isomers can be expected for the [1+1] macrocyclization product due to the low symmetry of the bis-naphthalene cleft: one with both clefts in a parallel orientation in the macrocycle (**1-syn**); the other one in an anti-parallel orientation (**1-anti**). After careful separation, the two isomers can indeed be isolated. ESI-MS confirmed both of them are the products of [1+1] macrocyclization between **2** and **3**. Their ^{1}H NMR spectra reveal high symmetry (Fig. 1), with some differences in the chemical shifts. However, the two isomers cannot be assigned only based on this information.

For **1-anti** and **1-syn**, the spatial arrangements of the two bis-naphthalene clefts are different. Butyl protons are in close proximity to aromatic protons for **1-anti**, but not for **1-syn**. Thus, different NOE effects may be expected for these two isomers. The ^{1}H,^{1}H-ROESY NMR experiments were thus performed (Fig. S1-S2), and all the signals in both isomers can be unambiguously assigned. Nevertheless, no significant differences on the NOE signals were observed for the two isomers. This may be due to that the two clefts are separated too far away by the urea groups, and thus the butyl protons and the aromatic protons are not within the effective distance of NOE effect.

Fortunately, single crystals (Fig. 2 and Fig. S3) of both isomers, suitable for X-ray crystallography, were obtained by slowly evaporating the solutions in the mixture of CH$_2$Cl$_2$ and CH$_3$CN. The crystal structures clearly show that the one with low polarity is **1-anti**, and the other one is **1-syn**. This is also consistent with their molecular structures: **1-anti** has an anti-parallel orientation of the two bis-naphthalene clefts, and the dipole moments are cancelled out, resulting in lower polarity. However, for **1-syn**, the dipole moments in the two clefts are parallel and thus enhanced, making **1-syn** to be more polar than **1-anti**.

Taking a closer look at the crystal structures, it reveals CH$_3$CN molecules in the cavities. For **1-anti**, in average eight solvent

molecules (six CH$_3$CN and two H$_2$O) are detected for one host molecule (Fig. S3), among which two CH$_3$CN molecules were trapped in the cavity by the urea groups with N-H···N hydrogen bonds (H···N distance: 2.39 and 2.43 Å). C-H···π interactions (H···π distance: 2.76~2.78 Å) between the methyl groups of the CH$_3$CN and the naphthalene panels of the host are also detected. The two CH$_3$CN molecules are in an anti-parallel orientation, perfectly satisfying their dipole moments. While for **1-syn**, in total 2.5 CH$_3$CN and one CH$_2$Cl$_2$ molecule are found for a single host molecule, but these solvent molecules are disordered (Figs. 2 and S3). Similar N-H···N hydrogen bonds (H···N distance: 2.25 and 2.52 Å) and C-H···π interactions (H···π distance: 2.52 - 2.89 Å) are also observed.

Does this binding between CH$_3$CN and the hosts exist in solution? Yes, but it is very weak: 200 eq. of CH$_3$CN cause only slight shift of the NH protons of **1-anti** or **1-syn** (Fig. S5-S6). In view of the two urea groups in the cavity, guests with two hydrogen bond acceptor atoms and appropriate size, such as 1,4-Dioxane (**4**), pyrazine (**5**), 2,3-dimethyl pyrazine (**6**), 1,4-Diazabicyclo[2.2.2]octane (**7**), and 1,2-dinitrobenzene (**8**) should be good guests in solution. Indeed, as shown in the NMR spectra (Fig. 3), the proton *c* of guest **4** undergoes
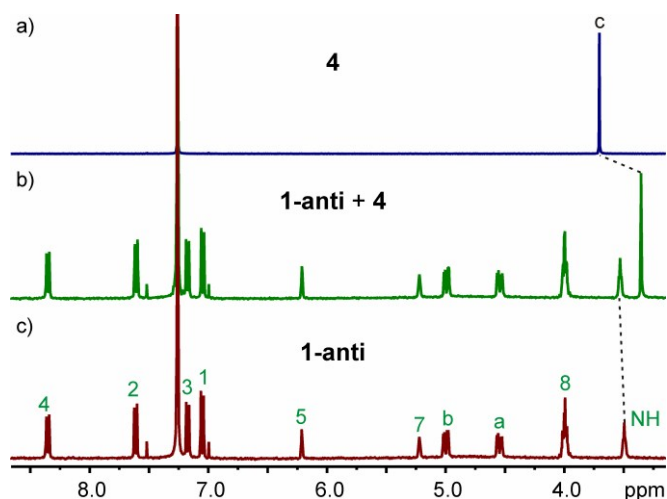
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Fig. 3 Partial ^{1}H NMR spectra (400 MHz, CDCl$_3$, 0.5 mM, 25 ^{o}C) of **1-anti**, **4**, and their equimolar mixture.

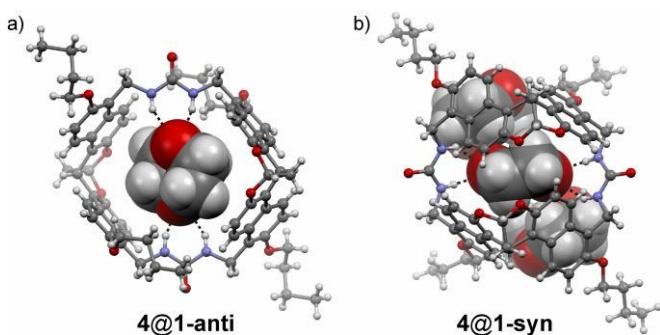**Fig. 4** X-ray single crystal structures of (a) **4@1-anti** and (b) **4@1-syn** obtained from the solution of CHCl$_3$ and CH$_2$Cl$_2$, respectively, in the presence of 1,4-dioxane (**4**). The guest molecules outside the cavities were removed for clarity.

significant upfield shift (-0.35 ppm) in the presence of one eq. **1-anti**. The NH protons of **1-anti** also slightly shift downfield (+0.03 ppm). This indicates that the guest sits inside the cavity and experiences a clear shielding effect, and the urea protons are involved in the hydrogen bonds with the oxygen atoms of the guest **4**. Similar binding phenomenon was observed for the host-guest pair of **4** and **1-syn** (Fig. S7). The complexations between **1** and **4** are further confirmed by the X-ray single crystal structures (Fig. 4 and S4). For both **1-anti** and **1-syn**, guest **4** fits perfectly into the cavity and is trapped there via strong N-H···O hydrogen bonds (H···O distance: 2.22 and 2.49 Å) and multiple C-H···π interactions (H···π distance: 2.72~2.90 Å). The guest is electrostatically complementary with the cavity of the host. The shape and the electronic nature of the cavity and the convergent functional groups all contribute to the binding.

Similar host-guest complexation was also observed for the guests **5**, **6**, **7**, and **8** (Fig. S8-S15). All complexes are in fast exchanges on the NMR timescale. Their binding stoichiometries were determined to be 1:1 for both **1-anti** and **1-syn** by Job's plots (Fig. S16-S19). In order to quantify these bindings and understand the preference, their binding

Table 1 Binding constants (M^{-1}) as determined by ^{1}H NMR titration (400 MHz, CDCl$_3$, 25 ^{o}C).[a]

	4	**5**	**6**	**7**	**8**
1-anti	220±7	307±10	16.9±0.4	12500±750	-[b]
1-syn	25.2±0.6	21.4±0.9	4.2±0.2	1470±40	51.4±1.2

a, the concentrations of the hosts are fixed at 0.5 mM; b, the binding constant is too small (< 1.0 M^{-1}) to be determined.
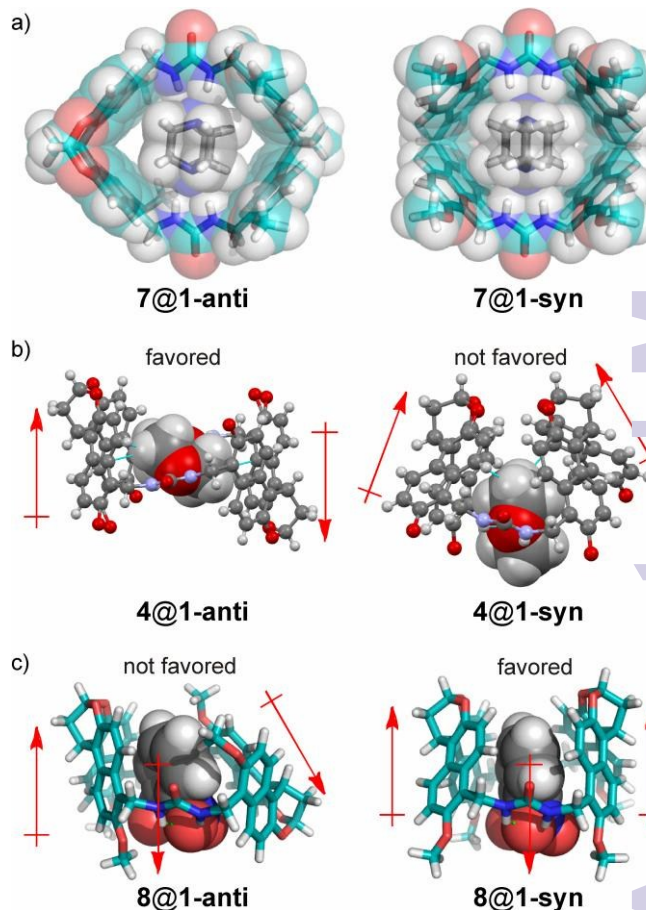

Fig. 5 (a) Energy-minimized structures of **7@1-anti** and **7@1-syn**; (b) X-ray single crystal structures of **4@1-anti** and **4@1-syn** and (c) energy-minimized structures of **8@1-anti** and **8@1-syn**. The dipole moments of the guests and the hosts were shown to explain the binding preference. The butyl groups on the hosts are removed or shortened for viewing clarity.

constants (listed in Table 1) were determined by NMR titration experiments (Fig. S20-S38).

For both **1-anti** and **1-syn**, 1,4-dioxane (**4**) and pyrazine (**5**) have similar binding affinities. Similar hydrogen bonds and C-H···π interactions as observed in Fig. 4 contribute to the binding between **5** and **1**. The introduction of methyl groups on pyrazine guest were expected to improve the binding affinity through filling the cavity better and offering possibilities for additional C-H···π interactions. However, 2,3-dimethyl pyrazine (**6**) turned out to be an unsuitable guest, presumably due to the incongruent match with the cavity. The guest **7** is the best, and the largest binding constants were observed: 12500 M^{-1} for **1-anti** and 1470 M^{-1} for **1-syn**. The molecular modelling (Fig. 5a) provides some clues to explain this: not only strong hydrogen bonds (2.0 - 2.2 Å) are formed,

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but also multiple C-H···π interactions through appropriately filling the cavity are detected. That is, the cavity and the urea groups cooperate to afford the strongest binding.

1-anti and **1-syn** have different binding preference. For guests **4**, **5**, and **7**, **1-anti** is much better than **1-syn**, showing 8 − 14 times larger binding constants. This corresponds to 5 − 6 kJ·mol^{-1} in the difference of Gibbs free energy. In contrast, for guest **8**, **1-syn** is much better than **1-anti**: the binding constant between **8** and **1-syn** is 51 M^{-1}, while the binding is too weak to be detected for **8** and **1-anti** (Fig. S36).

Why do these two configurational isomers show such different guest selectivity? It can be rationalized by analysing the dipole alignments of the hosts and the guests. **1-anti** is centrosymmetric: the two bis-naphthalene clefts are in an anti-parallel orientation, and their dipole moments are thus cancelled out. With centrosymmetric guests (such as **4** and **5**) inside the cavity, the cavity may still be adjusted, while maintaining the anti-parallel orientations of the two clefts' dipole moments. The symmetry of the whole complex is not changed. This is observed in the single crystal structures of CH$_3$CN@**1-anti** and **4**@**1-anti**, and the molecular model of **7**@**1-anti** (Fig. 5a and 5b). Therefore, guests **4**, **5**, and even **7** are very comfortable in the cavity of **1-anti**. If a guest with low symmetry, such as **8**, is bound in the cavity of **1-anti**, the perfect antiparallel alignment of the dipole moments is distorted (Fig. 5c). In addition, there is repulsion between the guest's dipole moment and the host's dipole moment. This disfavours the complex formation, resulting in lower binding affinity.

While for **1-syn**, the two clefts are in a parallel orientation, and the dipole moments repulse each other. But the flexibility of the urea linker still allows the two clefts to freely adjust to minimize repulsion. When symmetric guests, such as **4**, **5**, and **7**, are bound in the cavity, the dipole moments of the two clefts are more or less fixed, causing even stronger repulsion (Fig. 5b). While for **8**, the guest's dipole moment is in an antiparallel orientation to the host's, thus relieving the repulsion in the host's dipole moments and favouring the binding (Fig. 5c). Probably due to the same reason, guest **6** does not so obviously differentiate **1-anti** from **1-syn** as guest **5**, with respect to the ratios of their binding constants: 4:1 for **6**, while 14:1 for **5**.

In summary, we report the synthesis, configurational isomerism, and neutral guest recognition of two bis-urea macrocycles with a deep cavity. The functional urea groups were incorporated into the deep cavity, allowing them to cooperate to achieve "enzyme-like" binding. In addition, the dipole alignment is demonstrated to markedly influence on molecular recognition and presumably also on self-assembly.[10]

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