ORGANIC LETTERS

2004
Vol. 6, No. 2
181−184

Efficient Modulation of Hydrogen-Bonding Interactions by Remote Substituents

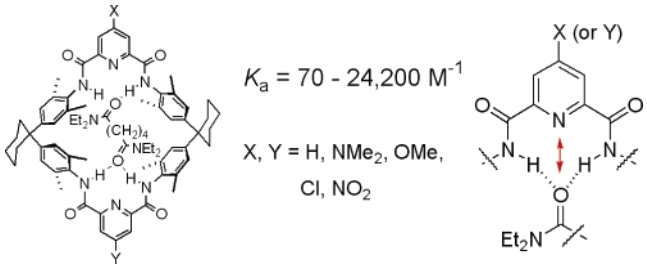
Sung-Youn Chang, Hung Sop Kim, Kyoung-Jin Chang, and Kyu-Sung Jeong*

Center for Bioactive Molecular Hybrids and Department of Chemistry, Yonsei University, Seoul 120-749, S. Korea

ksjeong@yonsei.ac.kr

Received October 7, 2003

ABSTRACT



A series of tetralactam macrocycles having different substituents were prepared, and their binding affinities for an adipamide guest were investigated in $CDCl_3$ by ^1H NMR titrations. The association constants strongly depend on the substituents, varying up to $\Delta\Delta G$ = 3.4 kcal/mol; electron-donating substituents (OMe, NMe_2) decrease the binding affinity, while electron-withdrawing groups (Cl, NO_2) increase it. These large substituent effects have been rationalized by secondary repulsions and partial perturbations of intramolecular hydrogen bonds.

A large variety of molecular motifs[1] have been developed and utilized over the last two decades to understand hydrogen-bonding interactions. Studies with these motifs have revealed that the stability of the complex depends not only on the number and type of the hydrogen bond but also on the arrangement of hydrogen-bonding donor and acceptor atoms. Furthermore, the strength of the hydrogen bonds can be conveniently modulated in several ways,[1,2] especially by electrochemical oxidation and reduction as nicely demonstrated by Rotello.[2]

Tetralactam macrocycles have been widely used as the ring component for the synthesis of interlocked molecules such as rotaxanes and pseudorotaxanes.[3] In the course of our own studies with the tetralactam macrocycles derived from pyridine-2,6-dicarboxamide scaffold,[4] we found that the affinities for dicarbonyl compounds were highly sensitive to the substituents at the para position of the pyridine rings. To carry out more systematic studies on the substituent effects, eight mono- and bis-substituted tetralactam macrocycles **2a-d** and **3a-d** bearing either electron-donating groups

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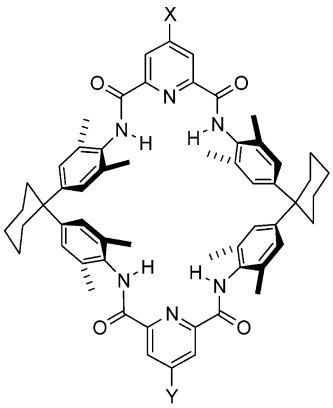
10.1021/ol035954j CCC: $27.50
Published on Web 12/17/2003

(NMe$_2$, OMe) or electron-withdrawing groups (NO$_2$, Cl) were prepared in addition to the unsubstituted one **1** (Figure 1).

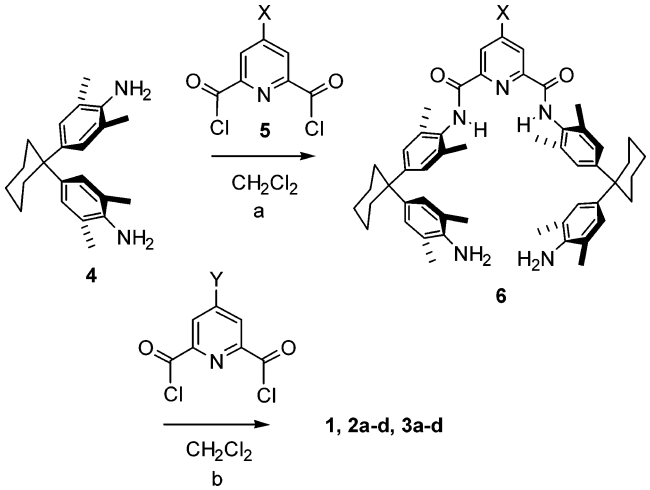


	X	Y
1	H	H
2a	H	NMe_2
b	H	OMe
c	H	Cl
d	H	NO_2
3a	NMe_2	NMe_2
b	OMe	OMe
c	Cl	Cl
d	NO_2	NO_2

Figure 1. Structures of tetralactam macrocycles **1**, **2a**−**d**, and **3a**−**d** and a diamide guest **7**.

The macrocycles **1**, **2a**−**d**, and **3a**−**d** were synthesized from a diamine **4**[5] and 4-substituted pyridine-2,6-dicarbonyl dichlorides **5**[6] according to the literature procedure for the preparation of **1** (Scheme 1).[5,7] Structures of the macrocycles were fully characterized by elemental analyses, NMR, and mass spectroscopy (see the Supporting Information).

Scheme 1. Synthesis of Tetralactam Macrocycles[a]



[a] Key: (a) *i*-Pr$_2$NEt, 0 °C to rt, 12−34%; (b) *i*-Pr$_2$NEt, 0 °C to rt, 23−66%.

A key molecular component of these macrocycles is the pyridine-2,6-dicarboxamide skeleton where intramolecular, weak N(pyridine)···HN(amide) hydrogen bonds are present.[8] As a result, all of the amide NHs in the macrocycles **1**, **2a**−**d**, and **3a**−**d** are inwardly oriented so that they can form simultaneously four hydrogen bonds, two pairs of bifurcated bonds, with an appropriate diamide guest. On the basis of computer modeling and preliminary binding studies, *N*,*N*,*N*′*N*′-tetraethyladipamide (**7**) was chosen as the guest for binding studies.

Binding behaviors of the reference macrocycle **1** toward the guest **7** were investigated in $CDCl_3$ at 23 ± 1 °C by ^{1}H NMR spectroscopy. The NH signal of **1** was gradually shifted from 8.95 to 10.25 ppm upon addition of **7**, indicative of the hydrogen bonding formation between the amide NH of **1** and the carbonyl oxygen of **7**. The association constant was estimated to be 780 M^{-1} by nonliner least-squares fitting[9] of the titration curve. On the other hand, the NH signal of **1** was little changed ($\Delta\delta$ < 0. 2 ppm) when excess (∼10 equiv) of a monoamide, *N*,*N*-diethylbutanamide, was added. This is clear evidence for the structure where two carbonyl oxygens at both ends of **7** are simultaneously bound to **1** in a bridging manner, one to each pyridine-2,6-dicarboxamide unit as shown in Figure 3. A Job plot[10] also supported a 1:1 complex between **1** and **7**, showing that maximum complexation occurs at a mole fraction of 0.5 (see the Supporting Information).

Association constants between substituted macrocycles **2a**−**d** and **3a**−**d** and **7** were determined under the same conditions, and the results are summarized in Table 1. The trend in the magnitudes of the association constants is apparent. That is, electron-withdrawing substituents (Cl, NO$_2$) increase the association constant, but electron-donating substituents (NMe$_2$, OMe) decrease it. For example, in a series of monosubstituted macrocycles **2a**−**d**, the association constants are 240 M^{-1} for **2a** (NMe$_2$), 550 M^{-1} for **2b** (OMe), 1360 M^{-1} for **2c** (Cl), and 4730 M^{-1} for **2d** (NO$_2$), respectively.

A series of bis-substituted macrocycles **3a**−**d** show more drastic variations in the association constants, ranging from 70 M^{-1} for **3a** (NMe$_2$) to 24 200 M^{-1} for **3d** (NO$_2$), corresponding to the difference in free energy ($\Delta\Delta G$) of 3.4 kcal/mol.

The large substituent effects on the binding affinities observed here may be attributed to the electrostatic repulsion between the pyridyl nitrogen of the macrocycle and incoming carbonyl oxygen of the guest (Figure 2). This repulsion can

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Table 1. Association Constants (K_a), Free Energy ($\Delta G°$), NH Chemical Shifts (δ_{Free}) of Free Macrocycles, and Observed (δ_{max} (obsd)) and Calculated (δ_{max} (calcd)) Maximum Chemical Shifts upon Complexation at 23 ± 1 °C in $CDCl_3$[a]

macrocycle	K_a (M^{-1})	$\Delta G°$ (kcal/mol)	δ_{free} (NH, ppm)	δ_{max} (obsd) (NH, ppm)	δ_{max} (calcd) (NH, ppm)
1 (H)	780	−3.9	8.95	10.25	10.36
monosubstituted					
2a (NMe_2)	240	−3.2	8.96, 9.12	10.02, 10.07	10.34, 10.35
2b (OMe)	550	−3.7	8.95, 9.00	10.16, 10.16	10.36, 10.34
2c (Cl)	1360	−4.2	8.94, 8.87	10.28, 10.26	10.35, 10.34
2d (NO_2)	4730	−5.0	8.95, 8.83	10.23, 10.25	10.34, 10.34
bis-substituted					
3a (NMe_2)	70	−2.5	9.12	9.74	10.36
3b (OMe)	410	−3.5	9.00	10.13	10.35
3c (Cl)	2430	−4.6	8.86	10.29	10.34
3d (NO_2)	24 200	−5.9	8.82	10.34	10.36

[a] Titrations were at least duplicated, and errors in K_a were within ± 10% for $K_a < 10^4$ M^{-1} and ± 25% for $K_a > 10^4$ M^{-1}. Initial concentrations of macrocycles and guest for titrations were 0.9−2 and 5−20 mM, respectively, depending on the magnitudes of the association constants and on their solubility in $CDCl_3$.

be considered as a new type of secondary hydrogen bonding interactions, originally proposed by Jorgensen.[11] Due to the direct resonance between substituents and the pyridyl nitrogen, the electron density at the nitrogen is highly sensitive to the nature of the substituents. In other words, the electron-withdrawing groups (NO_2, Cl) reduce the electron density at the nitrogen. Consequently, the electrostatic repulsion between the nitrogen and the oxygen decrease, thus increasing binding affinities. The exact opposite is true for the electron-donating groups (NMe_2, OMe). This explanation is also supported by liner free-energy relationship,[12] plotting $\log(K/K_H)$ vs σ_p^- (Figure 3b).[13] For a series of monosubstituted macrocycles, **2a**−**d** gave the reaction constant (ρ) of 0.63 with a nice correlation (R^2 =,0.996). As expected, ρ was found to be nearly twice as large (1.24) for a series of bis-substituted macrocycles **3a**−**d**.

Along with the electron density on the pyridyl nitrogen, the hydrogen-bonding donor ability of the amide hydrogen in the macrocycle may be partially responsible for the substituent effects. The electron-withdrawing substituents increase the donor ability, while the electron-withdrawing substituents decrease it. The association constants increase also in parallel with the donor abilities of the amide NHs of the substituted macrocycles.

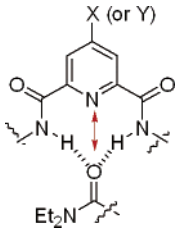

Figure 2. Schematic representation of possible electrostatic repulsions between the pyridyl nitrogen of macrocycles and the incoming carbonyl oxygen of guest.

In addition, possible perturbation of intramolecular hydrogen bonds upon the complex formation may be also

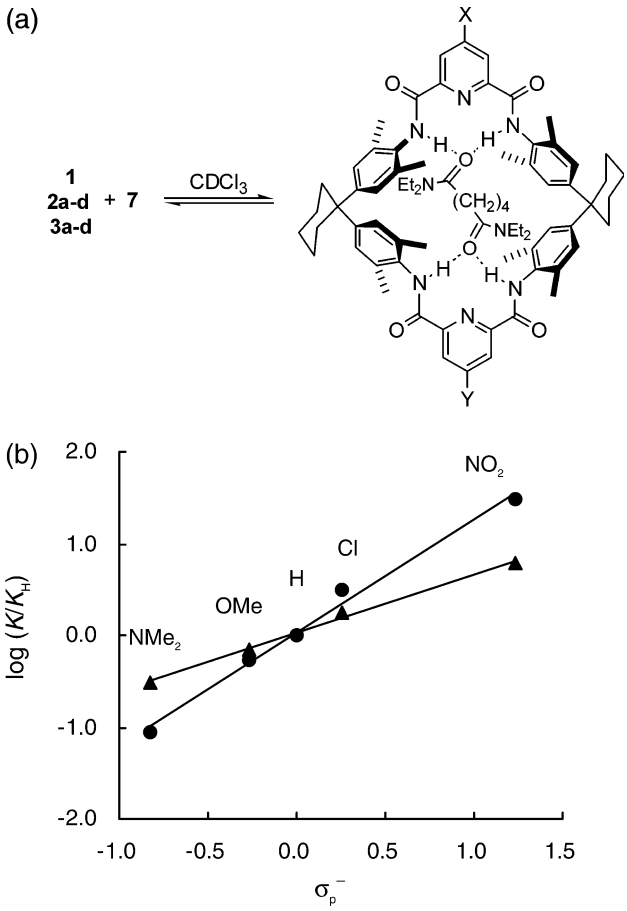

Figure 3. (a) Complexations between macrocycles **1**, **2a**−**d,** and **3a**−**d** and guest **7**. (b) Linear free energy plots of $\log(K/KH)$ vs σ_p^-. ▲: monosubstituted macrocycles, $Y = 0.63x + 0.023$, $R^2 = 0.996$. ●: bis-substituted macrocycles, $Y = 1.24x + 0.035$, $R^2 = 0.992$.

contributed to the substituent effects. As mentioned previously, intramolecular N(pyridine)···HN(amide) hydrogen bonds exist in the macrocycles. The relative positions of the NH signals of free macrocycles (δ_{free}) reflect well the presence and strength of intramolecular hydrogen bonds, as seen in Table 1.

The NH signal of the unsubstituted macrocycle **1** appears at 8.95 ppm in $CDCl_3$. The signals of **3a** (NMe_2, 9.12 ppm) and **3b** (OMe, 9.00 ppm) are downfield shifted, while those of the macrocycles **3c** (Cl) and **3d** (NO_2) appeared at 8.86 and 8.82 ppm, respectively. As the electron density on the pyridyl nitrogen increases, the NH signals are more downfield shifted because intramolecular hydrogen bonding interactions become stronger. On the other hand, the NH chemical shifts of all macrocycles when complexed become constant: calculated NH chemical shifts of the complexes, δ_{max} (calcd), in all cases are approximately 10.35 ppm, implying that local environments around hydrogen-bonded sections of the complexes are nearly identical regardless of the nature of the substituents. This situation can be envisioned when the intramolecular hydrogen bonds are partially perturbed until it is balanced with intermolecular hydrogen bonds between the macrocycles and the guest. The perturbation could be greater in the macrocycles containing stronger intramolecular hydrogen bonds, which results in the decrease of the association constants. Accordingly, the order of the association constants (**3d** > **3c** > **1** > **3b** > **3a**) is reverse to that of intramolecular hydrogen bonding interactions based on the relative positions of the amide NH signals.

In conclusion, we have demonstrated that using a series of tetralactam macrocycles and an adipamide guest the binding energy can be effectively modulated by remote substituents that alter considerably electron densities around hydrogen bonding sites. The capability of modulating intermolecular interactions is essential for the development of supramolecular devices or materials that can be responsive to external stimuli. We are currently pursuing this goal by replacing the pyridine unit of the macrocycle with other scaffolds, e.g., pyrazine, whose electron densities can be conveniently modified either by acid/base chemistry or by redox chemistry.

Acknowledgment. This work was financially supported by Korea Institute of Science & Technology Evaluation and Planning (M10213030001-02B1503-00310).

Supporting Information Available: Experimental procedures, physical properties, and spectroscopic data for the macrocycles **1**, **2a**−**d**, and **3a**−**d**; ^{1}H NMR titration data; and Job's plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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