

Cooperative and Selective Lithium Complexation of 2,11,13,22-Tetraaza-5,8,16,19-tetraoxa-1,12-dioxocyclodocosanes

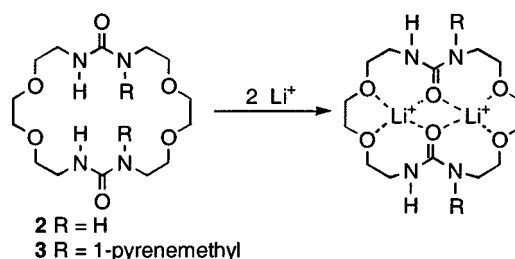
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ABSTRACT



Ureylene crown ethers **2** and **3** bind with 2 equiv of Li^+ cooperatively and selectively over other alkali metal ions such as Na^+ , K^+ , and Cs^+ . The binding constant for **3** was found to be 3.0×10^7 (L/mol)².

Since the discovery of crown ethers a few decades ago, the synthesis and chemistry of macrocyclic compounds has attracted considerable attention due to their unusual ability to act as hosts to both neutral and ionic species.¹ The study of host–guest phenomena provides a fundamental understanding of enzyme–substrate interactions in biological systems.² Recent investigations disclosed that the binding power of a host is governed by the size, the shape, the rigidity, and the noncovalent interactions of the cavity. Particularly important is the fact that highly flexible hosts often make binding entropically unfavorable. To tune the binding ability of a host, one should carefully design the

host with appropriate rigidity.³ Despite the fact that urea units and cyclic derivatives thereof are known to possess powerful ligating abilities which are due primarily to their highly polarized carbonyl groups, macrocycles incorporating ureas as the binding groups⁴ have received limited attention compared to their polyoxa, polyoxo, and polyaza congeners. Nevertheless, the synthesis and study of interesting macrocyclic hosts **1** and **2** have been reported independently.^{5,6} Recently, we have focused our research on ionic cooperative binding with receptors bearing polar rigid linkages.⁷ The

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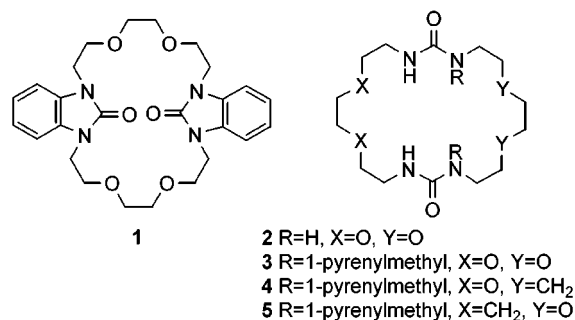
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Scheme 1

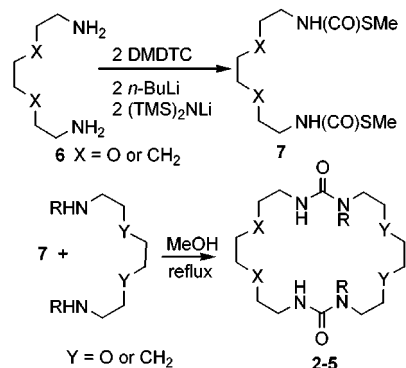


family of **1** and **2** attracts us because there are two potential binding sites separated by two urea groups (Scheme 1). We expected that the first binding occurring on one of the binding sites would establish electrostatic attractions toward the urea groups, inducing a conformational change that may directly affect the binding behavior of the second cavity.⁸ The mesomeric π -character of the C(O)–N group restricts the C–N bond rotation.⁹ This makes the urea unit a rigid-coplanar structure with the substituents in the sterically favored *Z,Z*-conformations. Between them, we are particularly intrigued with **2** not only because of its ligating power and rigidity but also the hydrogen bonding ability of the urea groups. The N–H portions on the urea groups may confer hydrogen-bonding interactions to other particular guests such as carboxylate anions.¹⁰ In this Letter, we report the discovery of the cooperative binding behavior of ureylene crowns (UC) **2** and **3** with lithium ions. Li⁺ is known to be an important ion in biological systems and has recently attracted the interest of many research teams.¹¹

Although the synthesis of **2** from the corresponding thiourea through the carbodiimide intermediate has been reported,⁶ we adopted a two-step synthetic sequence for **2–5** because this approach allows us to access the trisubstituted ureas **3–5**.¹² A typical procedure for the macrocyclization of **2–5** is described as follows: Treatment of diamine **6** with 2 equiv of *n*-BuLi and 2 equiv of LiN(SiMe₃)₂ at –78 °C followed by addition of (MeS)₂CO and subsequent warming to room temperature gave **7** in moderate yield. Coupling of **7** with another equivalent of diamine either in methanol,

ethanol, or propanol at reflux temperature in high dilution conditions afforded **2–5** (Scheme 2).

Scheme 2



Single-crystal X-ray crystallographic analysis of **2** shows a two-dimensional layer structure in which molecules of **2** are networked together through intermolecular hydrogen bonding between the urea groups. In addition, the relative orientations of the urea groups within each molecule are antiparallel with each other (Figure 1a). This result is

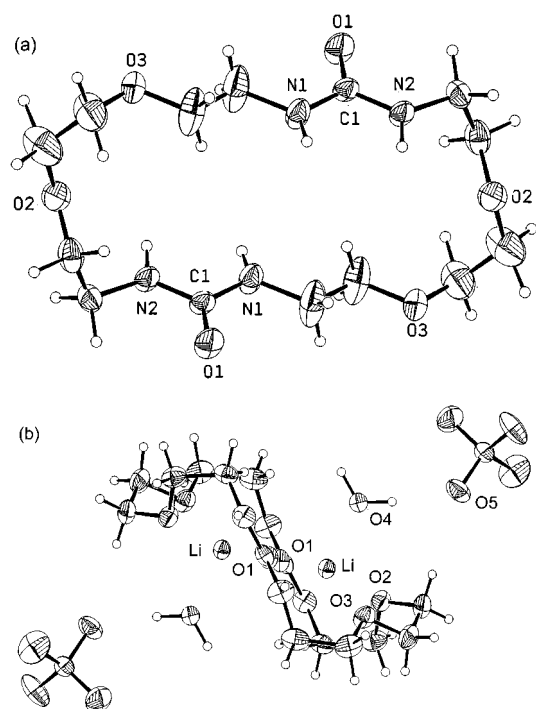


Figure 1. ORTEP drawings of (a) **2** and (b) **2**·Li₂²⁺.

consistent with the prediction of our molecular mechanics calculations.

Crystals for the complex of **2** with 2 equiv of Li⁺ ions were prepared by vapor diffusion of Et₂O into a solution of

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2 and $\text{LiClO}_4 \cdot 3\text{H}_2\text{O}$ in MeOH. The stoichiometry and the structure of the complex were confirmed by single-crystal X-ray analysis (Figure 1b). In the crystal lattice, **2** folds into an S-shape from the side view with the ureyleno carbonyl oxygen pointing inward and the N–H bonds pointing outward, creating two separated pockets ready for Li^+ ion binding. A water molecule occupies a fifth coordination site of the Li^+ ion.

The existence of the $2 \cdot \text{Li}_2^{2+}$ complex in solution was evidenced by ^{13}C NMR spectroscopy (Table 1). Although

Table 1. ^{13}C Chemical Shifts of UC **2**, UC $2 \cdot \text{Li}_2^{2+}$ and a 1:1 Mixture of UC **2** and LiClO_4 at -25°C in CD_3NO_2

	chemical shifts (ppm)		
UC 2	39.1	69.1	158.2
UC $2 \cdot \text{Li}_2^{2+}$	39.9	67.7, 72.3	161.9
UC $2 \cdot \text{Li}$ (1:1)	38.7, 39.4,	67.3, 68.6, 71.7	158.5, 161.4

the ^1H NMR spectra of **2** and $2 \cdot \text{Li}_2^{2+}$ in CD_3NO_2 are quite similar, their ^{13}C NMR spectra are substantially different.

The ^{13}C NMR spectrum of **2** shows three sets of resonance signals, including one signal at δ 39.1 ppm for the methylene carbons adjacent to the urea groups, one signal at δ 69.1 ppm for the two coincidentally equivalent oxymethylene carbons, and one signal at δ 158.2 ppm for the carbonyl carbons. Splitting of the signal at δ 69.1 ppm into two closely spaced resonance peaks at 70.4 and 70.7 ppm in CDCl_3 further confirms our assignments.

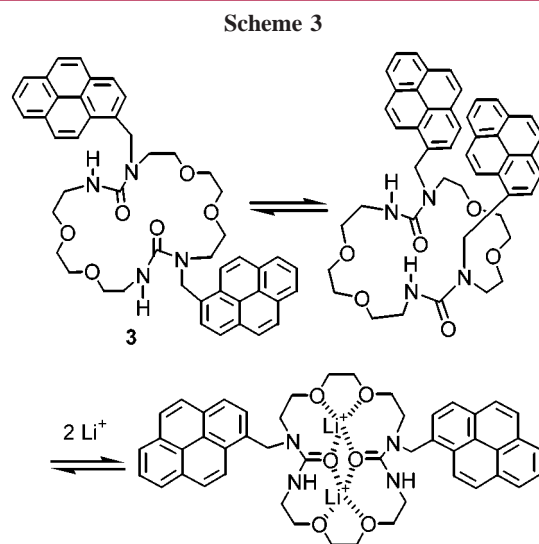
The spectrum of the $2 \cdot \text{Li}_2^{2+}$ complex shows four distinct resonance signals at 39.9, 67.7, 72.3, and 161.9 ppm. Signals at δ 67.7 and 72.3 ppm are attributed to the oxymethylene carbons whose chemical shifts are coincident before complexation. In addition, a significant downfield shift of 3.7 ppm for the carbonyl carbons is also anticipated in regard to the complex formation. The Li^+ ion bond in the cavity would polarize the carbonyl group, attracting the π -electron cloud toward the oxygen atom and therefore deshielding the carbonyl carbon with its consequent shift to a lower field.

To evaluate the cooperativity for Li^+ binding, the ^{13}C NMR spectrum of a 1:1 mixture of **2** and LiClO_4 was examined. If a strong cooperativity for Li^+ binding does exist, one would expect to observe mainly a spectrum arising from a mixture of **2** and $2 \cdot \text{Li}_2^{2+}$. On the other hand, if **2** preferentially forms a 1:1 complex, one would expect to see only one set of carbonyl carbon signals for $2 \cdot \text{Li}$. Unfortunately, the spectrum obtained at room temperature only shows coalesced signals of **2** with its complexes. To slow the fast lithium-ion exchange between **2** and its complexes, we carried out a low-temperature experiment at -25°C . Under these conditions, the spectrum is resolved into seven distinct signals in which four of them at 161.4, 71.7, 67.3, and 39.4 ppm are attributed to the $2 \cdot \text{Li}_2^{2+}$ complex. These signals are relatively sharp, and their integration ratios are in good agreement with the number of carbons. Perhaps due to the fast lithium ion exchange between **2** and the mono-

lithium complex, the other three remaining signals at 158.5, 68.6, and 38.7 ppm are relatively broad. Although the long relaxation time of ^{13}C NMR signals prevents us from accurate analysis of the equilibrium constants based on their integration, the comparable intensity of these two sets of signals suggested that the molar ratio of $2 \cdot \text{Li}_2^{2+}$ to **2** is about 1:1. These results imply the cooperativity of Li^+ ion complexation.

Complex $2 \cdot \text{Li}_2^{2+}$ formation has also been further evaluated by ^7Li NMR spectroscopy,¹³ using a method of continuous variation of **2** at a constant Li^+ concentration in CD_3NO_2 . In the absence of **2**, $^7\text{Li}^+$ ions show a magnetic resonance at $\delta = 0.03$ ppm. On gradually raising the relative amounts of **2**, the signal intensity of the uncomplexed Li^+ at 0.03 ppm drops while a new signal at -0.39 ppm for the complexed Li^+ increases. The maximum intensity of the signal at -0.39 ppm is reached at 1:2 $2/\text{Li}^+$ molar ratio, along with complete disappearance of the free Li^+ ion signal at 0.03 ppm. Further addition of **2** does not lead to any significant change of the spectrum. All these observations indicate a strong complexation of **2** with Li^+ to form the $2 \cdot \text{Li}_2^{2+}$ complex in solution. Unfortunately, Li^+ complexation is too strong to be accurately evaluated by ^7Li NMR methods.

To measure the complexation constant, pyrene groups are introduced to **3** and used as fluorescent probes. This is shown in Scheme 3. Before complexation with Li^+ ions, the



conformation of **3** is relatively flexible and therefore one would expect to observe the excimer signal of pyrenes in the fluorescence spectrum.¹⁴ However, once the cavities of **3** are filled up with Li^+ ions, the conformation of the crown structure would be restricted. According to our previous X-ray crystallographic analysis, we expected that the pyrene

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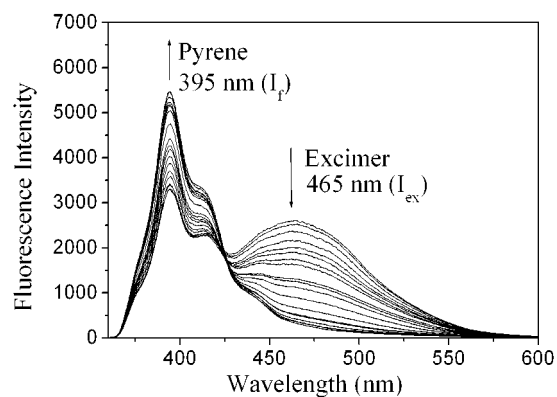


Figure 2. Fluorescence titration experiments of **3** at 2×10^{-6} M in CH_3CN with LiClO_4 as the titrant. Addition of LiClO_4 to a solution of **3** reduces the intensity of the excimer.

groups would point away from each other, and therefore the excimer signal should disappear.

Figure 2 shows the fluorescence spectra obtained from the titration experiments of **3** at 2×10^{-6} M in CH_3CN with LiClO_4 as the titrant. To minimize the intermolecular interactions, we adopted high dilution conditions such that within the experimental concentration range the values of I_f and I_{ex} are linearly proportional to the concentration of **3**. In addition, the ratio of I_f/I_{ex} is a constant, independent of the concentration. On addition of Li^+ ion to the solution of **3**, the relative intensity of the excimer signal (I_{ex}) at 465 nm gradually disappears while the intensity of the pyrene fluorescent signal (I_f) at 395 nm increases. Only one isobestic point is observed. Numerical analysis of the data revealed that the complex of $\mathbf{3} \cdot \text{Li}_2^{2+}$ is directly formed with a formation constant of 3.0×10^7 (L/mol)².¹⁵ In other words, the first lithium ion complexation substantially facilitates the second lithium ion binding in the same host.

On the other hand, **4** and **5** bind only 1 equiv of Li^+ with formation constants equal to 2.8×10^3 L/mol and 1.8×10^3 L/mol, respectively. Noteworthy is the stronger Li^+ binding of **4** than of **5**, indicating that Li^+ prefers to be accommodated into a cavity away from the nonpolar pyrene moieties.

(15) Formation of $\mathbf{3} \cdot \text{Li}_2^{2+}$ was confirmed by ESI-mass spectroscopy, ^7Li NMR titration, and fluorescence experiments. All related spectra and methods are provided in the Supporting Information.

The binding selectivity of **3–5** for different alkali metal ions has been studied by a competitive binding method. First of all, neither addition of Na^+ , K^+ , nor Cs^+ to a solution of **3–5** would significantly alter their fluorescence spectra. Therefore, we used the ratio of I_f/I_{ex} as an index for the Li^+ binding. The typical experimental concentrations of the solution we used are $[\text{UC}] = 2 \times 10^{-6}$ M and $[\text{LiClO}_4] = 5 \times 10^{-4}$ M in which the original $I_f/I_{ex} = 7–8$. In a series of competition experiments, addition of the same amounts of Na^+ , K^+ , or Cs^+ would not affect the ratios of I_f/I_{ex} for **3–5**, indicating the preference for Li^+ binding. In particular, the ratio of I_f/I_{ex} for **3** is not significantly altered even in the presence of a 100-fold excess of Na^+ and drops to only one-half in the presence of an 850-fold excess of Na^+ . All these observations suggested a high selectivity of **3** toward Li^+ binding.

Our experiments demonstrated the cooperative Li^+ ion binding behavior of **2** and **3**. As we showed before, dilithium complexation of **2** requires conformation change from the “anti-form” to the “S-form”. Therefore, we tentatively propose that the first Li^+ ion binding would readily direct the urea groups turning inward, prealigning the conformation of the crown ether into an “S-shape”, making the second Li^+ binding entropically, and perhaps enthalpically, more favorable.

In summary, our experiments demonstrated a novel approach for cooperative and selective Li^+ binding. This approach provides a new entry to this interesting field. Efforts are underway to extend the idea of cooperative binding to alkali metal/transition metal ion systems.

Acknowledgment. We thank the National Science Council and the Ministry of Education of the Republic of China for the financial support.

Supporting Information Available: ^1H and ^{13}C NMR spectra of **2–5** and $(\text{UC} \cdot \text{Li}_2)(\text{ClO}_4)_2$ complex (including single-crystal X-ray crystallographic data for **2** and $(\text{Li}_2) \cdot (\text{ClO}_4)_2$), spectral data for **2–5**, mathematical expression for the fluorescence experiments, and the ^7Li NMR spectra of **2** and **3** for the continuous variation experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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