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Helically Foldable Diphenylureas as Anion Receptors: Modulation of the Binding Affinity by the Chain Length

Min Jung Kim,[†] Hye-Won Lee,[†] Dohyun Moon,*[,‡] and Kyu-Sung Jeong*[,†]

Department of Chemistry, Yonsei University, Seoul 120-749, South Korea, and Pohang Accelerator Laboratory, San 31 Hyoja-Dong, Nam-Gu, Pohang, KyungBuk 790-784, South Korea

dmoon@postech.ac.kr; ksjeong@yonsei.ac.kr

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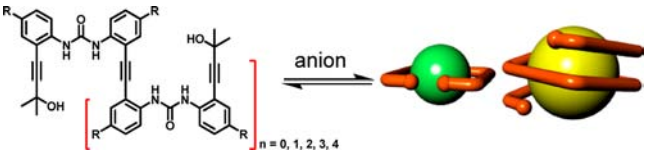
ABSTRACT



Using a series of diphenylureas capable of folding to helical conformations, the binding trends have been compared between two anions of different sizes, chloride and sulfate. The binding constant for the sulfate ion steadily increases from monomer to pentamer as the chain length increases, but for the chloride ion it increases up until the trimer and then reaches a plateau.

Anion recognition chemistry has been an active area of research for the past two decades, which includes the synthesis and characterization of anion receptors, sensors, transporters, and anion-induced assemblies.[1] Anion recognition was mostly based on H-bonding interactions, for which amide and urea groups were frequently incorporated to synthetic anion receptors. Wilcox et al.[2] and Hamilton et al.[3] demonstrated for the first time that (thio)ureas could form strong H-bonds with oxoanions such as carboxylates, sulfates, and phosphates. Since then, a large number of urea-based anion receptors[4,5] that contain two or more urea groups to achieve multiple H-bonds with target anions for the enhanced affinity and selectivity has been reported.

[†] Department of Chemistry, Yonsei University.
[‡] Pohang Accelerator Laboratory.

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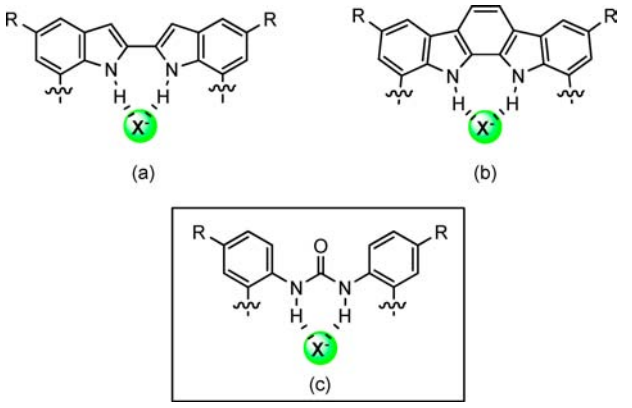
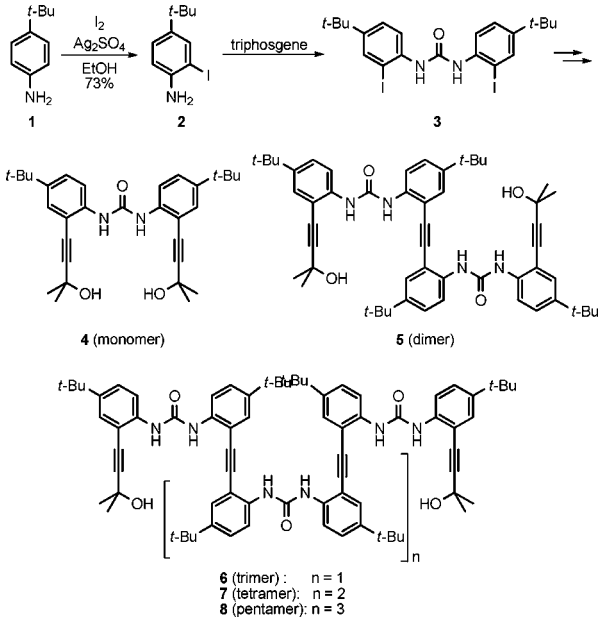


Figure 1. Comparison of hydrogen bonding patterns of (a) biindole, (b) indolocarbazole, and (c) diphenylurea units.

Compared with cyclic analogues, acyclic receptors in general show relatively weak binding affinities due to a larger entropy penalty upon the complex formation. This disadvantage could be in part mitigated if the acyclic receptors can adopt a (semi)stable ordered conformation, which in turn creates a binding cavity capable of accommodating a target guest. In this context, synthetic acyclic oligomers which fold to ordered arrays such as helices have been prepared and utilized as synthetic receptors.[6,7] We were also interested in the development of synthetic anion receptors based on acyclic linear oligomers such as oligoindoles[8] and oligoindolocarbazoles.[9] These oligomers could fold to helical conformations to form multiple H-bonds with anions. An obstacle was the multistep synthesis of the repeating units, a biindole and an indolocarbazole.

Scheme 1. Synthesis of **4**–**8**



Herein, we have designed a synthetically more accessible scaffold, a diphenylurea derivative **3**, that possesses the same H-bonding motif with two predecessors (Figure 1). Using this new scaffold, we have prepared a series of diphenylureas **4**–**8** which consist of one to five diphenylurea moieties, together with two hydroxyl groups at the ends. Diphenylureas **4**–**8** bind anions such as chloride and sulfate by multiple H-bonds, and the affinity increases as the chain length increases. There is however a noticeable difference in the increasing trend of the binding affinity between anions. For the small chloride ion, the association constant largely increases up until trimer **6** and then becomes nearly saturated, but for the large sulfate ion it steadily increases up to pentamer **8**.

The diphenylurea repeating units are linked through rod-like ethynyl spacers to prevent intramolecular H-bonds that often exist in oligourea-based anion receptors, thus reducing the association constants. It should be noted that the ethynyl spacer has been frequently used for the elongation of abiotic aryl foldamers because of the conformational simplicity and low energy barrier for folding.[6,7] The syntheses of diphenylureas **4**–**8** are summarized in Scheme 1. 4-*tert*-Butylaniline (**1**) was reacted with iodine in the presence of silver sulfate[10] to give 4-*tert*-butyl-2-iodoaniline (**2**) which was treated with triphosgene under basic conditions[11] to afford *N*,*N*′-di(4-*tert*-butyl-2-iodophenyl)urea (**3**). Using this new repeating scaffold, diphenylureas **4**–**8** were derived by sequential Sonogashira reactions[12] as described in the Supporting Information (SI).

Computer modeling studies have showed that, in the presence of the sulfate ion, diphenylureas **5**–**8** adopt

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helically coiled structures by the rotation of C−C bonds around ethynyl spacers (SI). For example, dimer **5** exists in an extended S-shaped conformation but folds into a coiled conformation upon binding a sulfate ion. Similarly, longer oligomers **6**–**8** exist in extended random conformations in the absence of an anion but adopt distorted helical structures wherein all of the existing NHs and OHs are simultaneously involved in H-bonding with a sulfate ion.

To find the binding mode in the solid state, we made numerous attempts of crystallization with various combinations of diphenylureas and anions. Fortunately, we obtained single crystals of complex **5**•$(Bu_4N)_2SO_4$ by slow diffusion of hexane to a CH_2Cl_2/hexane solution containing **5** (2.0 mM) and $(Bu_4N)_2SO_4$ (1.2 equiv). As shown in Figure 2, the sulfate ion is located in the middle of the cavity, forming two OH···O (sulfate) and four NH···O (sulfate) hydrogen bonds. Among them, two hydroxyl groups and three urea protons form normal H-bonds with distances of 2.67 and 2.69 Å for O···O and 2.72−2.84 Å for N···O, but one urea proton is a little more distant (3.05 Å), thus forming a weak H-bond.

Details of binding properties in solution were revealed by ^{1}H NMR spectroscopy. Tetrabutylammonium chloride and bis(tetrabutylammonium) sulfate were chosen as a representative anion for each of the small monatomic and large polyatomic anions, respectively. The binding behaviors were first examined in a relatively nonpolar medium, 10% CD_3CN/CD_2Cl_2, in order to find which protons are involved in the H-bonding with anions based on the complexation-induced shift (CIS, $\Delta\delta = \delta_{complex} - \delta_{free}$) of ^{1}H NMR signals. The results are summarized in Table 1. Several trends are clearly noticeable.

First, signals for all the NH and OH protons in each of the diphenylureas (**4**–**8**) were considerably shifted downfield upon addition of either the chloride or sulfate ion. In addition, the magnitudes of the CISs were larger in the case of the sulfate ion compared to the chloride ion, possibly due to the former forming stronger H-bonds than the latter. Second, the CIS value of the OH signal gradually decreased with the increasing chain length of **4**–**8** for the chloride ion. In addition, the most inner NH proton NH(1) in each of the diphenylureas was the most downfield shifted, and the most outer NH(*n*), the least shifted. This result indicates that the bound anion is located in the middle of the helical strand and therefore the outer OH and NH protons are distanced away from the entrapped anion, forming relatively weak H-bonds in longer oligomers. Third, the CIS values of NH protons in pentamer **8** by chloride binding were smaller than those of the corresponding NH protons in shorter ones, but they were comparable in the case of the sulfate ion. A plausible explanation is that the relative strength of the individual H-bond may decrease when multiple H-bonds form with a small monatomic anion, possibly due to electrostatic repulsions between adjacent donor atoms. However, this effect could be much smaller in the case of the larger polyatomic sulfate ion. Finally, the chemical shift changes in the longer oligomers **6**–**8** were negligible when more than 1 equiv of chloride and sulfate ions were added (Figure 3), clearly indicating that 1:1 complexes are formed even in the presence of excess anions.

Table 1. Complexation-Induced Shifts (CIS, $\Delta\delta$(ppm) = $\delta_{complex} - \delta_{free}$) of ^{1}H NMR signals for OHs and NHs[a] in 10% (v/v) CD_3CN/CD_2Cl_2 at 25 °C

anion	host	OH	NH(1)	NH(2)	NH(3)	NH(4)	NH(5)
Cl^-	**4**	2.03	1.87				
	5	1.57	1.80	0.96			
	6	1.53	1.24	1.17	0.89		
	7	0.56	1.22	1.46	1.27	0.89	
	8	0.47	1.15	1.05	1.05	0.87	0.57
SO_4^{2-}	**4**	3.48	2.37				
	5	3.38	2.78	2.12			
	6	–[b]	3.00	1.84	1.73		
	7	–[b]	2.98	2.82	–[b]	–[b]	
	8	–[b]	2.97	2.55	2.51	1.15	0.68

[a] Numbering of NH signals in **4** to **8** was assigned from center NH(1) to terminal NH(*n*). [b] ^{1}H NMR signals were broaden out on the baseline.

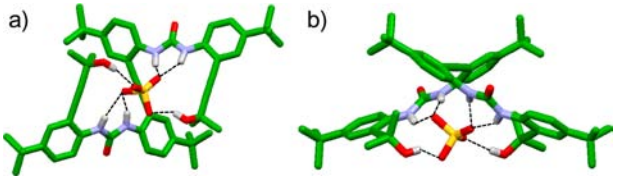

Figure 2. Two views of the crystal structure for complex **5**•$(Bu_4N)_2SO_4$. H-bonds are marked by dashed lines. All the CH H-atoms and tetrabutylammonium cations are omitted for clarity.

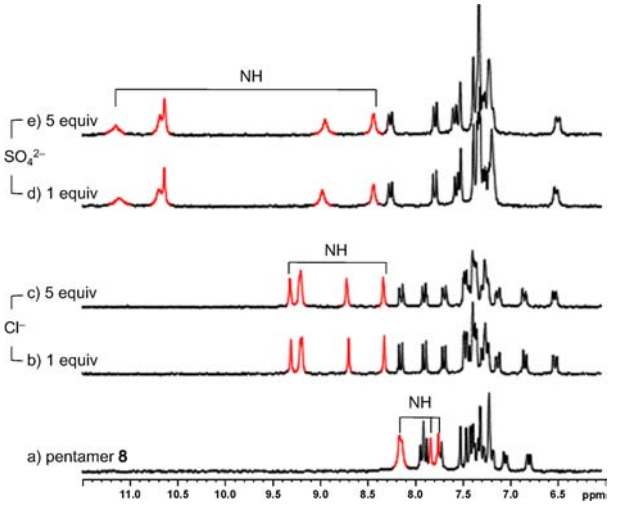

Figure 3. Partial ^{1}H NMR spectra (250 MHz, 10% CD_3CN/CD_2Cl_2) of **8** in the presence of (a) no anions, (b) Bu_4NCl (1 equiv), (c) Bu_4NCl (5 equiv), (d) $(Bu_4N)_2SO_4$ (1 equiv), and (e) $(Bu_4N)_2SO_4$ (5 equiv).

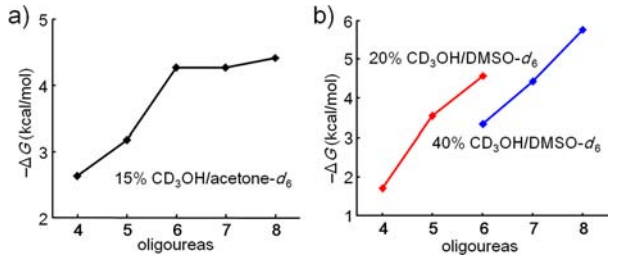

Figure 4. Plots of the binding free energy ($-\Delta G$, kcal/mol) of **4**–**8** with (a) chloride ion and (b) sulfate ion.

Quantitative binding affinities were determined by the ^{1}H NMR titrations in polar media containing a protic solvent, MeOH. Under these conditions, ^{1}H NMR spectra of longer oligomers **6**–**8** are competely concentration-independent in the range of 0.5–5.0 mM, suggesting that the aggregation of ureas is negligible (SI). For accurate comparison, the amount of methanol was chosen for the association constant to be in the range of 10^1 and 10^4 M^{-1}, and the results are summarized in Table 2 and Figure 4. First, the association constants of the chloride ion with **4**–**8** were evaluated in 15% (v/v) CD_3OH/acetone-d_6. The association constants of **4**, **5**, and **6** increased by 3- to 7-fold for an additional urea unit and then reached a plateau (Figure 4a). It should be mentioned that all of the existing NH protons of **7** and **8** showed downfield shifts during the titrations, but the magnitudes of the CIS values were smaller compared with those of **6**. This result suggests that, relative to **6**, more NH protons of **7** and **8** participate in H-bonding with the chloride ion but the strength of individual H-bond may be weakened as mentioned above, which is possibly responsible for the comparable binding affinity of **6**, **7**, and **8**.

Next, the association constants between **4**–**8** and the sulfate ion were determined in much more H-bond-competitive media 20% and 40% (v/v) CD_3OH/DMSO-d_6. The binding affinity steadily increases from monomer **4** to pentamer **8** by Gibbs free energy (ΔG) of 1.0–1.9 kcal/mol for each increment of the diphenylurea unit (Figure 4b).

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Table 2. Association Constants ($K_a \pm 10\%$, M^{-1}) between Diphenylureas **4**–**8** and Anions[a] (Cl^- and SO_4^{2-}) at 25 °C

	Cl^- [a]	SO_4^{2-} [a]	
host	15% CD_3OH/acetone-d_6	20% CD_3OH/DMSO-d_6	40% CD_3OH/DMSO-d_6
4	85	17	–[b]
5	210	390	–[b]
6	1340	2230	270
7	1350	$>1.0 \times 10^4$	1690
8	1720	$>1.0 \times 10^4$	16100

[a] Anions were used as the tetrabutylammonium salts. [b] Not determined.

The sulfate ion contains four oxygen atoms with a tetrahedral geometry as H-bond acceptors, each of which can form two or three H-bonds. As a result, the sulfate ion can accommodate multiple H-bonds,[13] up to twelve in pentamer **8**, without noticeably lessening the strength of individual hydrogen bonds to enhance the net affinity.

In conclusion, using a series of helically foldable diphenylureas, we have demonstrated that the affinity and selectivity of an anion can be modulated by tuning the chain length. Given that these helical foldamers possess an internal cavity for anion binding, they could be further modified to form a channel-like assembly, thus enabling the transport of anions such as chloride in the lipid membrane.

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Supporting Information Available. Synthesis and characterization of new compounds, binding studies and Job's plot, X-ray details, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.