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Molecular Recognition of Dicarboxylate Ions by Bis-phenylureas Derived from a New Dicarboxylic Acid.

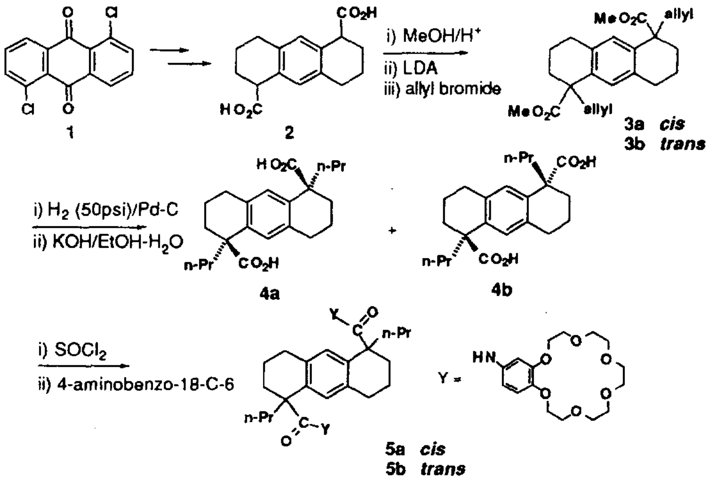
Kyu-Sung Jeong*, Jong Woo Park and Young Lag Cho

Department of Chemistry, Yonsei University
Seoul 120-749, Korea

Abstract: A new dicarboxylic acid **4** was synthesized from 1,5-dichloroanthraquinone (**1**) and modified to ditopic receptors for binding of diammonium and dicarboxylate salts by multiple hydrogen bonds. The *cis* and *trans* isomers of **4** were assigned by the relative binding affinities of the bis(crown ether) derivatives, **5a** and **5b** to alkyl diammonium dipicrates. The association constants (K_a) between *p*-substituted bis-phenylureas and adipate vary from 5 x 10^2 to 2 x 10^4 M^{-1} in DMSO-d_6, depending on substituents in the phenyl ring.

Molecular recognition of neutral and ionic substrates by artificial receptors is an area of much current interest. One of the most important tasks in this area is the design and construction of a receptor that possesses complementary size, shape and functionality to a target substrate. Recently, several groups have reported neutral receptors with (thio)urea functionality for binding of the anionic species, halide, carboxylate, phosphate, and sulfonate through hydrogen-bonding interactions.[1] We here report the synthesis of a new dicarboxylic acid **4a** that can potentially serve as a molecular building block for various artificial receptors.[2] Additionally, we have prepared a series of *p*-substituted bis-phenylureas from the diacid **4a**, and studied substituent effects in binding to dicarboxylates in a polar solvent, DMSO-d_6.

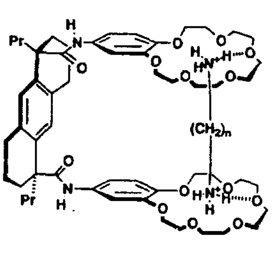
Scheme 1



The synthesis of dicarboxylic acid **4** is outlined in Scheme 1. An intermediate diacid **2** was prepared from 1,5-dichloroanthraquinone (**1**) by a known procedure[3] in 65% yield as a diastereomeric mixture. After esterification of diacid **2** in methanol, the resulting diester was subjected to allylation to afford a 1: 1 mixture of *cis* and *trans* diesters, **3a** and **3b**, in a 74% total yield. The two isomers (R_fs in silica gel, hexanes/EtOAc = 5:1(v/v); less polar isomer 0.44, more polar isomer 0.36) were separated by flash column chromatography. Hydrogenation followed by hydrolysis of each isomer gave the corresponding diacids **4a** and **4b** quantitatively. To assign *cis* and *trans* isomers, the diacids **4a** and **4b** were modified to the bis(crown ether)s, **5a** and **5b**, of which the *cis* isomer may show much stronger binding affinities to alkyl diammonium salts than the *trans* isomer, because two crown ether units in the *cis* isomer can bind diammonium salts in a cooperative way as shown below.[4] The binding properties of bis(crown ether)s and alkyl diammonium dipicrates were examined by solid-liquid extractions and the results are shown in Table 1.

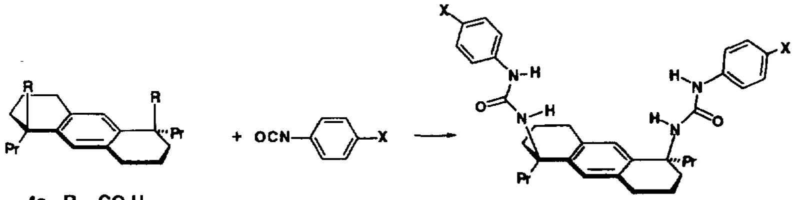
Table 1. The Results of Solid-Liquid and Liquid-Liquid Extractions.[5]

		$^+H_3N - (CH_2)_n - NH_3^+$		
extraction method	bis(crown ether)	n = 3	n = 4	n = 5
solid-liquid (equiv)	**5a** (from more polar)	0.91	0.58	0.85
	5b (from less polar)	0.43	0.17	0.46
liquid-liquid (%)	**5a** (from more polar)	17	26	31
	5b (from less polar)	3	5	4



All of the diammonium salts studied here are hardly soluble in $CDCl_3$ without **5a** and **5b** and thus dissolution occurs mostly by complexation. Clearly bis(crown ether) **5a** derived from more polar isomer **3a** much more efficiently dissolves the diammonium dipicrates in $CDCl_3$. More quantitative information can be obtained by Cram's liquid-liquid extraction method.[6] The bis(crown ether) **5a** extracts 17-31% of diammonium salts into $CHCl_3$ from aqueous solution, while **5b** extracts only 3 - 5%. The association constants based on these extraction values, assuming 1:1 complexes, are approximately 10 to 20-fold higher on complexation of bis(crown ether) **5a** and each diammonium dipicrate, relative to bis(crown ether) **5b**.[5a] We concluded therefore that the two ester groups of the more polar diester **3a** are in a *cis*, while those of less polar diester **3b** are in a *trans* relationship.

Scheme 2



4a R = CO_2H
6 R = C(O)Cl
7 R = NH_2

8a X = NO_2
8b X = CO_2Et
8c X = Cl
8d X = H
8e X = OMe
8f X = NMe_2

After treating the *cis*-diacid **4a** with thionyl chloride, Curtius rearrangement (NaN_3/acetone-H_2O, Δ, then H_3O^+) of the resulting **6** afforded the corresponding diamine **7** which was coupled with a series of *p*-substituted phenyl isocyanates to give the corresponding bis-ureas **8a-8f** in a 24 - 94% yield (Scheme 2).[7] The association constants (K_a) between ureas and bis(tetrabutylammonium) dicarboxylates were determined in DMSO-d_6 by nonlinear least-squares fit of the ^1H NMR titration data, and the results are summarized in Table 2.

Table 2. Association Constants (K_a ± 10%, M^{-1}) between Ureas and Carboxylates in DMSO-d_6 at 297 ±1 K

urea	carboxylate	K_a (M^{-1})	urea	carboxylate	K_a (M^{-1})
9	*n*-butyrate	320	**8a** (X = NO_2)	adipate	21800
8d(X = H)	glutarate	1430	**8b** (X = CO_2Et)	"	6840
"	adamantane		**8c** (X = Cl)	"	2360
"	1,3-dicarboxylate	2580	**8d** (X = H)	"	1710
"	isophthalate	920	**8e** (X = OMe)	"	1400
"	adipate	1710	**8f**(X = NMe_2)	"	510

Two NH signals of free ureas appear at 8.06 - 9.19 ppm for phenyl-NH and 6.04 - 6.56 ppm for alkyl-NH in DMSO-d_6, depending on the substituents on phenyl ring. Addition of dicarboxylates (5 mM) to ureas (2 mM) gave large downfield shifts of the urea NHs, $\Delta\delta$ = 2-3 ppm for phenyl-NH and 1-2 ppm for alkyl-NH, and the saturation curve from changes of each NH signal gave the same association constant (K_a) within 5% error. These observations indicate that both NHs are involved in hydrogen bonding on the formation of same complex. On the comparison of dicarboxylates with three carbon spacers between the two carboxyl groups, binding affinities are increasing in order of isophthalate, glutarate and adamantane 1,3-dicarboxylate. This may be attributed mainly to the rotational entropic advantage of adamantane 1,3-dicarboxylate and less basicity of isophthalate on complexation with urea, compared to glutarate. As a reference system of two hydrogen bonds, mono-urea **9** and tetrabutylammonium butyrate was tested and the association constant is 320 M^{-1} in DMSO-d_6. All of the association constants of bis-phenylurea **5d** and aliphatic dicarboxylates are > 10^3 M^{-1} , indicating two urea functions cooperatively bind to dicarboxylate through four hydrogen bonds by 1:1 complexation as shown in **10**. This was confirmed by a Job's plot which gave a maximum at mole ratio 0.5.[8]

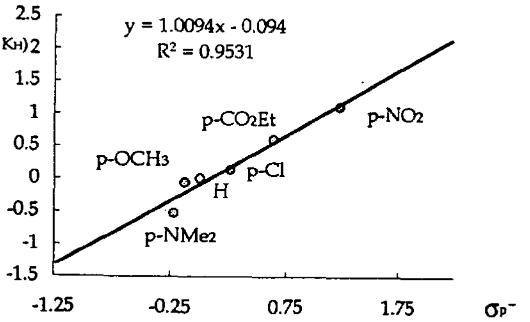
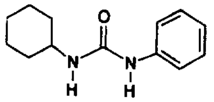


Figure 1. Linear free energy relationship of log (K_X/K_H) vs. σ_p^-.



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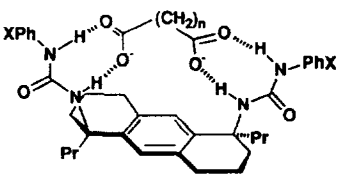

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In order to investigate the substituent effects on hydrogen bonding, a series of *p*-substituted bis-phenylureas were examined. A trend in magnitudes of association constants is apparent; electron-withdrawing groups at the *para* position of the phenyl ring increase the binding affinity while electron-donating groups decrease it. As an example of extremes, the urea **8a** with nitro group shows ~ 40-fold higher association constant than **8f** with *N,N*-dimethylamino group, even though both ureas **8a** and **8f** form the same number of hydrogen bonds with adipate. The large difference reflects how strongly the complex stability depends on acidity-basicity of hydrogen-bonding donor and acceptor. The linear free energy relationship between association constants (K_a) and substituent constants (σ) was examined.[9] A plot of log (K_X/K_H) *vs.* σ_p gave $\rho = 0.967$ and $r^2 = 0.918$. A better correlation was observed by using σ_p^- ($\rho = 1.01$ $r^2 = 0.953$), which is shown in Figure 1.[10] These results suggest that the hydrogen-bonding interaction strongly depends on the resonance and electronic effects of substituents, and the relative binding affinities in this system can be predicted by the acidity of substituted aniliniums or phenols.

In conclusion, the large variations in K_as were observed on complexation of *p*-substituted bis-phenylureas and adipate through hydrogen-bonding interactions, indicating that the right match-up of acidity-basicity between binding partners, not just the number of hydrogen bonds, determines complex stability.

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5. The bis(crown ether) **5a** or **5b** (0.7 mL, 5.0 mM in $CDCl_3$) and excess solid diammonium dipicrate (10 equiv) were employed for solid-liquid extractions at ambient temperature. The amounts dissolved were determined by ^{1}H NMR integration of aromatic peaks and errors were within 10%. The liquid-liquid extractions were performed with 1.5 mL of **5a** or **5b** (3.0 mM in $CHCl_3$) and 1.5 mL of diammonium dipicrate (0.50 mM in deionized water). All experiments were triplicated at 297 ± 1K. The amounts extracted were determined by changes in UV absorbance (370 nm) of picrates in aqueous solution and errors were less than 3% in the extraction percentages.
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7. The yields were not optimized and all ureas were fully characterized by ^{1}H NMR, FT-IR, and MS spectra. Mp: **8a** 182-183 °C; **8b** 170-172 °C; **8c** 171-172 °C; **8d** 172-173 °C; **8e** 134-136 °C; **8f** 168-170 °C.
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