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A New Quadruple Hydrogen-Bonding Module Based on Five-Membered Heterocyclic Urea Structure

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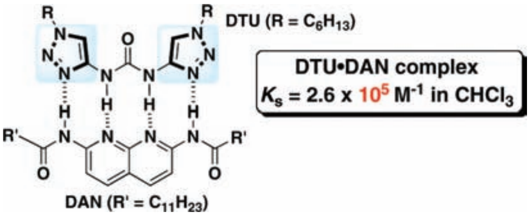
ABSTRACT



N,N'-Di-4-triazolylurea (DTU) has developed as a new ADDA module and DTU forms a stable ADDA•DAAD heterocomplex with 2,7-diamido-1,8-naphthyridine (DAN) ($K_s = 2.6 \times 10^5$ M^{-1} in $CHCl_3$). The K_s value of the complex between DTU and DAN is 100-fold greater than that of the complex between N,N'-di-2-pyridylurea and DAN due to replacement of a pyridine ring with a 1,2,3-triazole ring.

Supramolecular architectures obtained by quadruple hydrogen-bonding modules with linear arrays have become an important research topic in supramolecular chemistry such as supramolecular polymers, nanofibers, and stimuli-responsive assembles.[1] Among these quadruple hydrogen-bonded systems,[1] highly stable heterocomplexes with high selectivity can offer diversity and great potential in this field.[2,3]

Zimmerman reported ADDA (A = hydrogen-bond acceptor, D = hydrogen-bond donor) modules inspired by a nucleobase. Ureidoguanine (**UG**)[2a,b] and 7-deazaguanine urea (**DeUG**)[2c,d] form highly stable ADDA•DAAD heterocomplexes with 2,7-diamido-1,8-naphthyridine (**DAN**)[4] as the complementary DAAD module ($K_s > 10^7$ M^{-1} in $CDCl_3$), and exhibit weak self-association (K_{dim} for **UG** $\approx 2.3 \times 10^2$ M^{-1} and K_{dim} for **DeUG** $= 8.8 \times 10^2$ M^{-1} in $CDCl_3$).[5] Their conformers with ADDA arrays can be well-preorganized with the use of an intramolecular hydrogen bond,[6] and other unfavorable conformers and tautomers are disfavored. The

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(1) For reviews, see: (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding (Berlin)* **2000**, *96*, 63. (b) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5. (c) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071. (d) Wilson, A. J. *Soft Matter* **2007**, *3*, 409. (e) Dankers, P. Y. W.; Meijer, E. W. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2047. (f) de Greef, T. F. A.; Meijer, E. W. *Nature* **2008**, *453*, 171. (g) de Greef, T. F. A.; Smulders, M. M. J.; Wolffs, M.; Schenning, A. P. H. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Rev.* **2009**, *109*, 5687. (h) Lee, C. C.; Grenier, C.; Meijer, E. W.; Schenning, A. P. H. J. *Chem. Soc. Rev.* **2009**, *38*, 671.

(2) (a) Park, T.; Zimmerman, S. C.; Nakashima, S. *J. Am. Chem. Soc.* **2005**, *127*, 6520. (b) Park, T.; Todd, E. M.; Nakashima, S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2005**, *127*, 18133. (c) Ong, H. C.; Zimmerman, S. C. *Org. Lett.* **2006**, *8*, 1589. (d) Kuykendall, D. W.; Anderson, C. A.; Zimmerman, S. C. *Org. Lett.* **2009**, *11*, 61.

(3) With regard to application to a supramolecular polymer, it has been suggested that the ideal association constant for useful degrees of polymerization is comparable to or greater than $\sim 10^5$ M^{-1} in $CHCl_3$.[1d−g]

(4) (a) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Org. Chem.* **2006**, *71*, 375. (b) Todd, E. M.; Quinn, J. R.; Park, T.; Zimmerman, S. C. *Isr. J. Chem.* **2005**, *45*, 381.

(5) While ureidopyrimidinone (**UPy**) and deazapterin (**DeAP**) can provide ADDA arrays and form highly stable heterocomplexes with **DAN** ($K_s > 10^7$ M^{-1}), these systems compete with highly stable self-associated dimers with DDAA arrays ($K_{dim} > 10^7$ M^{-1}), see: (a) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 810. (b) de Greef, T. F. A.; Ercolani, G.; Ligthart, G. B. W. L.; Meijer, E. W.; Sijbesma, R. P. *J. Am. Chem. Soc.* **2008**, *130*, 13755. (c) de Greef, T. F. A.; Ligthart, G. B. W. L.; Lutz, M.; Spek, A. L.; Meijer, E. W.; Sijbesma, R. P. *J. Am. Chem. Soc.* **2008**, *130*, 5479. (d) Wang, X.-Z.; Li, X.-Q.; Shao, X.-Q.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T.; Chen, Y.-Q. *Chem.—Eur. J.* **2003**, *9*, 2904. (e) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710.

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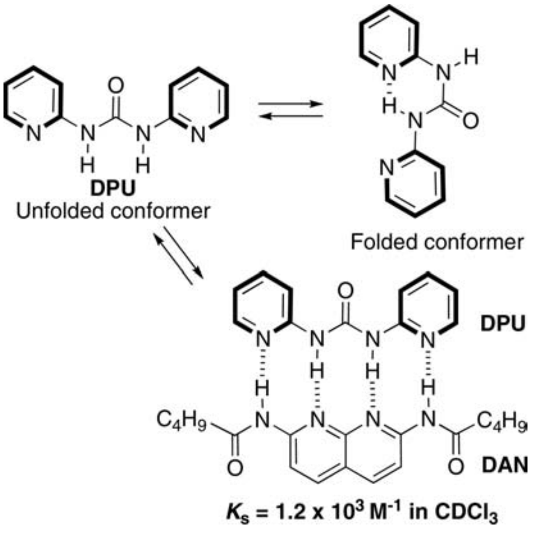
utility of the **UG•DAN** complex has been demonstrated in supramolecular block copolymers and supramolecular polymer blends.[7]

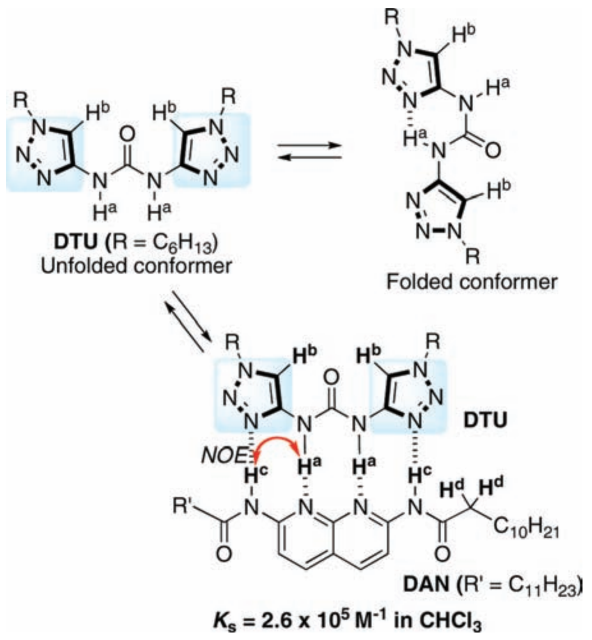
Scheme 1



As another type of ADDA module, *N*,*N*′-di-2-pyridylurea (**DPU**) has been studied in detail (Scheme 1).[8] Unfortunately, the K_s value of **DPU** with **DAN** ($K_s = 1.2 \times 10^3$ M^{-1} in $CDCl_3$) is much lower than the predicted value since **DPU** prefers to form a folded conformer, which is stabilized by intramolecular hydrogen-bonding.[8,9] Therefore, the intramolecular hydrogen-bonding of **DPU** in the folded conformer must be broken prior to the complexation with **DAN**.

We have been interested in development of quadruple hydrogen-bonding modules based on five-membered heterocyclic urea structures because these have a clear advantage over 2-pyridylurea structures in regard to providing linear multiple hydrogen-bonding arrays.[10] We considered that six-membered heterocyclic ureas such as 2-pyridylurea structures would be destabilized as a result of steric repulsion due to the shorter distance between 3-H in the pyridine ring and the oxygen on the urea carbonyl substitute. Thus, their conformational equilibrium was biased toward the folded conformer that was stabilized by the intramolecular hydrogen-bonding. In contrast, some five-membered heterocyclic ureas, such as 4-oxazolylurea derivatives, were capable of forming unfolded conformers, since the unfavorable interactions in six-membered heterocyclic ureas are reduced in five-membered heterocyclic ureas.[10] Recently, we applied our concept to development of a new DDAA module, ureidoimidazo[1,2-a]pyrimidine (**UImp**).[11] This module forms a highly stable homodimer ($K_{dim} > 1.1 \times 10^5$ M^{-1} in $CDCl_3$) without competition from undesired hydrogen-bonded dimers.

Scheme 2



In this paper, we report *N*,*N*′-di-4-triazolylurea (**DTU**) as a new ADDA module based on a five-membered heterocyclic urea structure (Scheme 2). The 1,2,3-triazole ring system in **DTU** is easily synthesized via the Huisgen 1,3-dipolar cycloaddition, which is known as the click reaction.[12] To the best of our knowledge, **DTU** is the first example of an ADDA module that forms a highly stable heterocomplex with **DAN** ($K_s = 2.6 \times 10^5$ M^{-1} in $CHCl_3$) without preorganization of its conformation by intramolecular hydrogen-bonding. The K_s value of **DTU•DAN** complex is 100-fold greater than that of **DPU•DAN** complex due to replacement of the pyridine ring with the 1,2,3-triazole ring.

DTU was easily synthesized in four steps from commercially available reagents (Scheme 3). Triazole **1** was prepared in a one-pot synthesis via the Huisgen 1,3-dipolar cycloaddition from 1-hexylbromide in 92% yield,[13] and hydrolysis to give acid **2** in 89% yield. **DTU** was then prepared from **2** via the Curtius rearrangement with diphenylphosphoryl azide (DPPA) in 60% yield.[14]

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(6) A hydrazide-based ADDA module reported by Li is also well-preorganized with the use of intramolecular hydrogen-bonding and exhibits highly stable ADDA•DAAD heterocomplexes with **DAN** ($K_s = 6.0 \times 10^5$ M^{-1} in $CDCl_3$) and weak self-association ($K_{dim} = 5.5 \times 10^1$ M^{-1} in $CDCl_3$), see: Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128.

(7) (a) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 13986. (b) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 14236. (c) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 11582.

(8) (a) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475. (b) Singha, N. C.; Sathyanarayana, D. N. *J. Chem. Soc., Perkin Trans. 2* **1997**, 157. (c) Lüning, U.; Kühl, C.; Uphoff, A. *Eur. J. Org. Chem.* **2002**, 4063. (d) Sudha, L. V.; Sathyanarayana, D. N. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1647.

(9) Sartorius, J.; Schneider, H.-J. *Chem.—Eur. J.* **1996**, *2*, 1446.

(10) Hisamatsu, Y.; Fukumi, Y.; Shirai, N.; Ikeda, S.; Odashima, K. *Tetrahedron Lett.* **2008**, *49*, 2005.

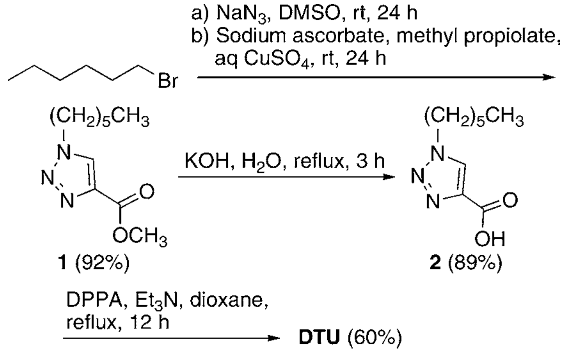
(11) Hisamatsu, Y.; Shirai, N.; Ikeda, S.; Odashima, K. *Org. Lett.* **2009**, *11*, 4342.

(12) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249.

(13) Kacprzak, K. *Synlett* **2005**, *6*, 943.

(14) Vereshchagin, L. I.; Kirillova, L. P.; Shafeev, M. A. *Russ. J. Org. Chem.* **1998**, *34*, 258.

Scheme 3. Synthesis of **DTU**



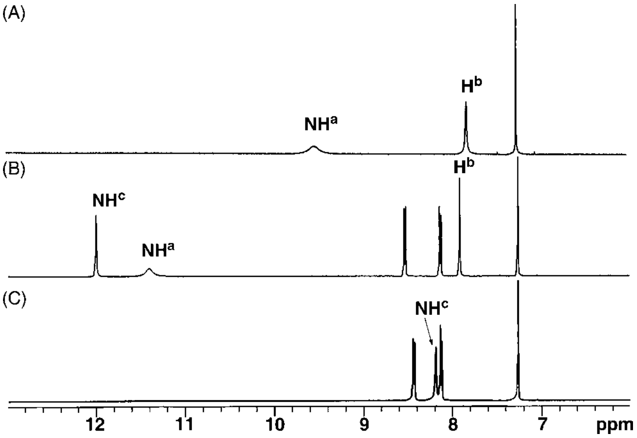


Figure 1. Partial ^{1}H NMR spectra (500 MHz) of (A) **DTU** (10 mM), (B) **DTU** (10 mM) + **DAN** (10 mM), and (C) **DAN** (10 mM) at 25 °C in $CDCl_3$.

First, the self-association of **DTU** was investigated by ^{1}H NMR. In a dilution study of **DTU** in $CDCl_3$ from 45 mM to 0.40 mM, NH^a and CH^b proton signals were shifted upfield, respectively. This indicated the self-association of **DTU** in $CDCl_3$ by intermolecular hydrogen bonds involving NH^a protons. The change in the chemical shift ($\Delta\delta$) of NH^a between 45 mM and 1.0 mM was 0.72 ppm, and the NH^a broadened below 1.0 mM. The change in the chemical shift ($\Delta\delta$) of CH^b from 45 mM to 0.40 mM was 0.13 ppm and the K_{dim} value was determined to be $(7.1 \pm 0.6) \times 10^2$ M^{-1} by the nonlinear least-squares curve-fitting method.[15,16] When the $CDCl_3$ solution of **DTU** (10 mM) was cooled from 25 to −50 °C, both NH^a ($\Delta\delta = 0.76$ ppm) and CH^b ($\Delta\delta = 0.10$ ppm) proton signals showed downfield shifts that were consistent with self-association. Furthermore, the splitting of NH^a and CH^b proton signals, which indicated the folded conformer,[8a,10] was not observed. Similar variable-temperature ^{1}H NMR spectra were obtained in a dilute concentration of **DTU** (0.80 mM). On the other hand, the major conformer of **DPU** is the folded one.[8] Indeed, in the ^{1}H NMR spectra of **DPU** in $CDCl_3$, proton signals of urea NH and aromatic 3-H in the pyridine ring disappear due to broadening at 25 °C, and two pairs of split proton signals of the urea NH and 3-H were observed at −40 °C, since these protons are not equivalent in the folded conformer.[8a] These results suggested the minimal contribution of the formation of folded **DTU** dimer[17] and the proposed major dimeric structure of **DTU** should be unfolded one (see Supporting Information).

Next, the formation of a heterocomplex between **DTU** and the complementary DAAD module **DAN** was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ (Figure 1). At a 1:1 ratio of **DTU** (10 mM) and **DAN** (10 mM), a significant downfield shift was observed for the urea NH^a of **DTU** ($\Delta\delta = 1.88$ ppm) and the amide NH^c of **DAN** ($\Delta\delta = 3.82$ ppm). These changes in the chemical shift support the formation of a **DTU•DAN** complex via multiple hydrogen bonds involving NH^a and NH^c protons. The stoichiometry of the complex between **DTU** and **DAN** was confirmed to be 1:1 by a Job plot.[18] NOE contact was observed between the NH^a of **DTU** and NH^c of **DAN**. In addition, the ESI mass spectrum shows molecular ion peaks of **DTU•DAN** (*m*/*z*: 887.6 [**DTU** + **DAN** + H]$^+$). These results strongly indicate that **DTU** forms a quadruple hydrogen-bonded heterocomplex with **DAN** by ADDA•DAAD arrays, as shown in Scheme 2. The formation of a **DTU•DAN** complex was also supported by the DFT calculation at the B3LYP method with a 6-31+G** basis set. The distance of hydrogen-bonding $NH^a\cdots N$ and $NH^c\cdots N$ was estimated to be 2.1 Å and 2.0 Å, respectively. When **DAN** (1.0 mM) was titrated with **DTU** (0 − 3.0 equiv) by ^{1}H NMR, significant downfield shifts were observed for both the NH^c ($\Delta\delta = 3.9$ ppm) and CH^d ($\Delta\delta = 0.26$ ppm) proton signals and these were almost saturated upon the addition of 1.0 equiv of **DTU**. In a dilution study of a 1:1 mixture of **DTU** and **DAN** from 20 mM to 0.4 mM,[2] no clear changes were observed in the chemical shift values of NH^a and NH^c proton signals.[19] This shows that the **DTU•DAN** complex persists at a low concentration.

We investigated the binding property in the **DTU•DAN** complex by UV/vis spectroscopy in $CHCl_3$ at 25 °C (Figure 2). Upon the addition of **DTU** (0 − 3.0 equiv) to **DAN** (20 μM), the absorption intensity of **DAN** at 353 and 370 nm increased with an isosbestic point at 349 nm. Based on the change in the absorption intensity at 353 nm, the stability constant of a 1:1 complex between **DTU** and **DAN** was determined to be $(2.6 \pm 0.2) \times 10^5$ M^{-1} by the nonlinear least-squares curve-fitting method.[15,20] The K_s value of **DTU** with **DAN** is 100-fold greater than that of **DPU** ($K_s = 1.2$

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(15) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

(16) When we tried to determine the K_{dim} value of **DTU** based on chemical shift changes of urea NH^a proton signals at the concentration from 1.0 mM to 45 mM, the K_{dim} value gave large error due to insufficiency of the chemical shift data at lower concentration range (<1 mM).

(17) The K_{dimer} value of **DTU** was higher than those for general folded dimers with DA•AD arrays ($K_{dim} < 3 \times 10^2$ M^{-1} in $CDCl_3$)[6,8a] see: (a) EArcher, A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139. (b) McGhee, A. M.; Kilner, C.; Wilson, A. J. *Chem. Commun.* **2008**, 344. (c) Lafitte, V. G. H.; Aliev, A. E.; Horton, P. N.; Hursthouse, M. B.; Bala, K.; Golding, P.; Hailes, H. C. *J. Am. Chem. Soc.* **2006**, *128*, 6544.

(18) Job, P. *Ann. Chim. Appl.* **1928**, *9*, 113.

(19) For a 1:1 mixture of **DTU** and **DAN** at a concentration of less than 0.4 mM, the NH^a proton signal of **DTU** disappeared due to broadening. Assuming that there is less than 10% dissociation at 0.4 mM, the K_s value of **DTU•DAN** was estimated to be a lower limit of 1.1×10^5 M^{-1}.[2]

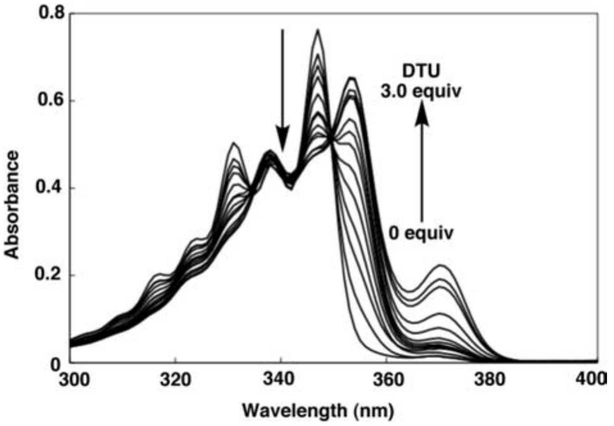

Figure 2. Changes in the absorption spectra of **DAN** (20 μM) in $CHCl_3$ at 25 °C upon addition of **DTU** (0−3.0 equiv).

$\times 10^3$ M^{-1} in $CDCl_3$) by replacement of the pyridine ring with the 1,2,3-triazole ring.

To predict the ΔG values of linear multiple hydrogen-bonded complexes, Zimmerman developed a formula based on an empirical method.[21] This formula takes into account several variables including intramolecular hydrogen bonds that are broken before complexation (e.g., 2-pyridylureas).[8] The ΔG_{298} value calculated for **DTU•DAN** complex from the formula was estimated to be −7.0 kcal mol^{-1}, when the variable for the intramolecular hydrogen bond was not used. This calculated ΔG_{298} value was similar to the experimental value ($\Delta G_{298} = -7.4$ kcal mol^{-1}). This supports the notion that **DTU** is suitable for use as an ADDA module and preorganization is not needed to give a linear ADDA array.

In conclusion, we have developed a new ADDA module based on the five-membered heterocyclic urea structure. *N*,*N'*-Di-4-triazolylurea (**DTU**) forms a highly stable ADDA•DAAD complex with **DAN** ($K_s = 2.6 \times 10^5$ in $CHCl_3$) without preorganization. Due to replacement of the pyridine ring with a 1,2,3-triazole ring, the K_s value of **DTU•DAN** complex is 100-fold greater than that of **DPU•DAN** complex. This result shows that the 1,2,3-triazole system via the click reaction is useful for obtaining components of multiple hydrogen-bonding modules. Our concept would contribute to development of promising quadruple hydrogen-bonding modules without the competition of undesired folded conformers and tautomers. Since limited examples of DADD modules have been reported,[8c,22] we are currently studying the development of novel DADD module based on the five-membered heterocyclic urea structure.

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Supporting Information Available: Details of the synthesis and characterization for all new compounds, the complexation studies by NMR measurements, ESI-MS measurement and DFT calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Due to small absorption intensity changes (370 nm) of **DAN** at the lower concentration range of **DTU** (<1.0 equiv), it was difficut to determine the K_s value.

(21) Quinn, J. R.; Zimmerman, S. C.; Del Bene, J. E.; Shavitt, I. *J. Am. Chem. Soc.* **2007**, *129*, 934.

(22) DADD•ADAA arrays exhibit low affinity ($K_s < 10^3$ M^{-1} in $CHCl_3$) since DADD modules contain 2-pyridylurea structurs, see: (a) Taubitz, J.; Lüning, U. *Eur. J. Org. Chem.* **2008**, 5922. (b) Quin, J. R.; Zimmerman, S. C. *Org. Lett.* **2004**, *6*, 1649.