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Hydrogen-Bonded DeUG·DAN Heterocomplex: Structure and Stability and a Scalable Synthesis of DeUG with Reactive Functionality

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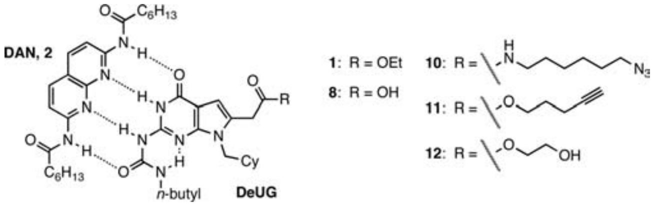
ABSTRACT



A convenient, scalable synthesis of the supramolecular building block 7-deazaguanine-based urea (DeUG) is reported. Incorporation of reactive moieties (DeUG azide 10 and alkyne 11 for copper-catalyzed azide-alkyne cycloadditions, "click chemistry") and a demonstration of transesterification (DeUG glycol, 12) highlights the versatility. X-ray structures of DeUG and a DeUG·DAN heterocomplex were obtained. K_{assoc} for the 1·2 heterocomplex was estimated to be 2 × 10^8 M^{-1} in chloroform.

Designed supramolecular interactions continue to play a central role in the development of novel and functional nanoscale devices and materials. Partly inspired by DNA base-pairing, as well as the strength and predictability of hydrogen-bonding interactions, many efforts to expand the supramolecular toolkit have focused on heterocyclic compounds that form hydrogen-bonded dimers or heterocomplexes.[1] Among quadruply hydrogen-bonded systems, the ureidopyrimidinone (UPy) unit is especially notable.[2] Other examples include our own urea of deazapterin (DeAP)[3] and a recently reported urea of cytosine.[4] Despite the advances made in this field, there is a recognized need to develop synthetically accessible, high-affinity, high-fidelity[5] (orthogonal) hydrogen-bonding modules that are readily and easily linked to surfaces, nanoparticles, polymers, and other compounds and materials.[6]

Recently, we reported the development of a new, hydrogen-bonding module based on a 7-deazaguanine urea (DeUG)

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(1) For reviews, see: (a) Sessler, J. L.; Jayawickramarajah, J. *Chem. Commun.* **2005**, 1939–1949. (b) Sivakova, S.; Rowan, S. J. *Chem. Soc. Rev.* **2005**, *34*, 9–21. (c) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5–16. (d) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426. (e) Sherrington, D. C.; Taskinen, K. A. *Chem. Soc. Rev.* **2001**, *30*, 83–93. (f) Krische, M. J.; Lehn, J.-M. *Struct. Bonding* **2000**, *96*, 3–29. (g) Meléndez, R. E.; Carr, A. J.; Linton, B. R.; Hamilton, A. D. *Struct. Bonding* **2000**, *96*, 31–61. (h) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63–94. (i) Kato, T. *Struct. Bonding* **2000**, *96*, 95–146. (j) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229–2260.

(2) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirshberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601–1604.

(3) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710–9711.

(4) 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*, 6544–6545.

(5) Todd, E. M.; Quinn, J. R.; Park, T.; Zimmerman, S. C. *Isr. J. Chem.* **2005**, *45*, 381–389.

(6) (a) Feldman, K. E.; Kade, M. J.; de Greef, T. F. A.; Meijer, E. W.; Kramer, E. J.; Hawker, C. J. *Macromolecules* **2008**, *41*, 4694–4700. (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*, 13755–13764.

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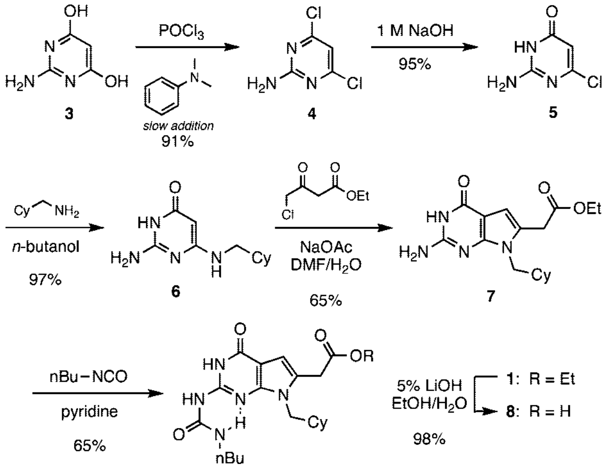
unit.[7] DeUG was designed as a synthetically versatile, robust analogue of UG, a guanosine-derived urea, which formed highly stable quadruply hydrogen-bonded complexes with 2,7-diamido-1,8-naphthyridine (DAN).[8] Although the reported synthesis of DeUG served our needs at the time, it suffered from low overall yields (ca. 15% over 4 steps) and required the use of capricious hydrolysis conditions. Moreover, the structure did not easily accommodate further synthetic elaboration.

Herein, we report a convenient and scalable synthesis of DeUG bearing a synthetic handle for further elaboration, including clickable functionality. Detailed complexation studies are reported including an X-ray analysis revealing the solid-state structure of DeUG and a DeUG•DAN heterocomplex, the latter the first reported structure of a quadruply hydrogen-bonded heterocomplex.

Relatively minor changes to the previously reported synthesis resulted in an approximately 3-fold improvement in overall yield at reduced cost. As shown in Scheme 1, analytically pure carboxylic acid functionalized DeUG **8** was readily prepared on multigram scale (>10 g) in an overall yield of approximately 35% over six steps without the need to employ column chromatography for purification.

Scheme 1. DeUG Synthesis

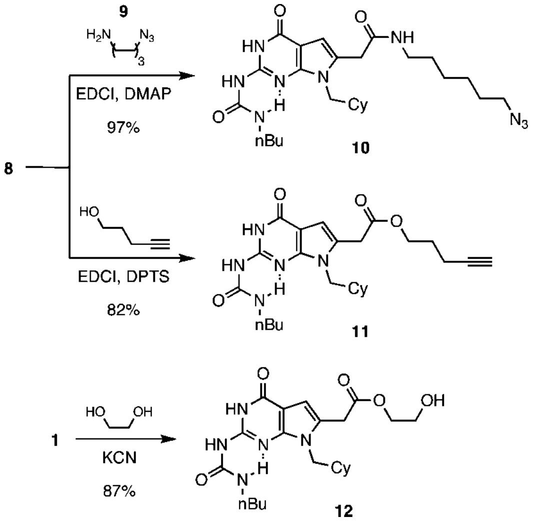


Commercially available pyrimidine **3** was treated with phosphorus oxychloride with slow addition of *N*,*N*-dimethylaniline to afford dichloropyrimidine **4** in excellent yield. Other more environmentally benign bases, such as triethylamine, can also be used for this transformation, albeit with minor reductions in yield.[9] Hydrolysis of **4** in refluxing aqueous NaOH gave chloropyrimidinone **5**, also in excellent yield.[10] Although both **4** and **5** are commercially available, they are easily and less expensively prepared as described. Beginning from advanced intermediate **5** offers only a small improvement in overall yield (ca. 5%) at significant cost. Displacement of the chloride by cyclohexanemethylamine proceeds smoothly in refluxing 1-butanol with triethylamine. Cyclocondensation via slow addition of ethyl 4-chloroacetoacetate in DMF/H$_2$O with sodium acetate afforded deazaguanine analogue **7**.[11]

Formation of the urea of 7-deazaguanine using 1-butyl isocyanate in pyridine gave **1** in moderate yield. Lithium hydroxide mediated hydrolysis of the ethyl ester in 1:1 ethanol/H$_2$O affords analytically pure carboxylic acid functionalized DeUG **8** in excellent yield.

As a demonstration of the ease with which **8** can be functionalized with "clickable" groups, both alkyl azide and terminal alkyne variants were prepared using standard carbodiimide coupling protocols. Additionally, **1** can readily be transesterified using ethylene glycol with potassium cyanide[12] to provide the 2-hydroxyethyl ester variant, thus expanding the reactivity profile of DeUG (Scheme 2).

Scheme 2. DeUG Functionalization



^{1}H NMR dilution studies of DeUG **1** in deuterated chloroform were performed as previously reported.[7] Both the N1−H and the aromatic C7−H resonances gave adequate signal-to-noise ratios. However, the N2−H and N3−H resonances showed substantial broadening at low concentrations and could not be used to determine a dimerization constant (K_{dimer}). K_{dimer} values of 520 M^{-1} and 700 M^{-1}

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(7) Ong, H. C.; Zimmerman, S. C. *Org. Lett.* **2006**, *8*, 1589–1592.

(8) (a) Park, T.; Mayer, M. F.; Nakashima, S.; Zimmerman, S. C. *Synlett* **2005**, 1435–1436. (b) Park, T.; Zimmerman, S. C.; Nakashima, S. *J. Am. Chem. Soc.* **2005**, *127*, 6520–6521. (c) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 11582–11590. (d) For an initial report of a DAN derivative in molecular recognition, see: Lüning, U.; Kühl, C. *Tetrahedron Lett.* **1998**, *39*, 5735–5738.

(9) Appleton, W. C.; Parziale, P. A. Eur. Pat. WO9507265, 1995.

(10) Burgdorf, L. T.; Carell, T. *Chem. Eur. J.* **2002**, *8*, 293–301.

(11) The major side product during the cyclocondensation step was found to be diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate (DESS), which is presumably formed via self-condensation of ethyl 4-chloroacetoacetate. Slow addition of the β-keto ester modestly decreases the amount of DESS formed; however, attempts at further reducing this side reaction proved unsuccessful and had minor impact on the yield of **7**.

(12) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790–791.

(average, 610 M^{-1}) were determined via standard nonlinear least-squares regression analysis following N1−H and C7−H chemical shift changes, respectively (see Supporting Information).[13]

Orthorhombic crystals of DeUG ethyl ester **1** suitable for X-ray analysis were obtained via recrystallization from acetone. Although some disorder was observed in both the cyclohexanemethyl and ethyl groups, the structure revealed an interesting zipper-like (vernier-type) hydrogen-bonding assembly via repeating lactam-urea contacts and confirmed the preorganized acceptor-donor-donor-acceptor (ADDA) motif (Figure 1a). To accommodate the steric bulk of the molecule, the average plane defined by the heterocycles for each of any two hydrogen-bonded DeUG units lie at a 58.6° angle to one another (Figure 1b), with the lactam-urea N−H···O hydrogen-bond length being 1.90(0) Å (angle, 165°) and the urea-lactam N−H···O hydrogen-bond length being 1.99(8) Å (angle, 173°). The intramolecular N−H···N hydrogen bond, which preorganizes DeUG into the desired motif, was found to be 2.01(4) Å (angle, 133°).

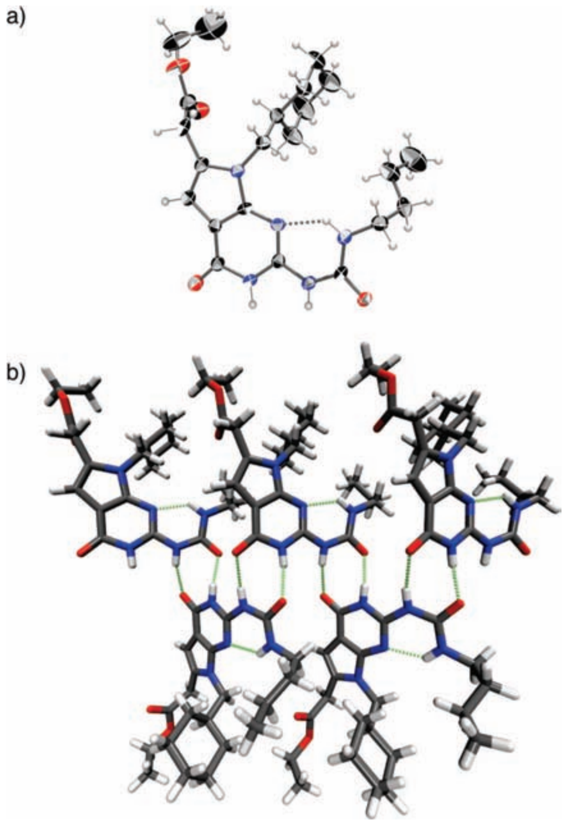

Figure 1. (a) ORTEP representation of **1**. Thermal ellipsoids represent 50% probability. (b) X-ray structure (licorice representation) of **1** showing the zipper-like hydrogen bonding assembly.

The association constant (K_{assoc}) of heterocomplex **1·2** in chloroform was expected to be beyond the limit of detection by ^1H NMR titration studies.[7] Therefore, isothermal titration calorimetry (ITC) was employed (Figure 2). Upon titration of DAN into DeUG at 25 °C in chloroform, the best fit curve gave $K_{assoc} = 1.3 \times 10^7$ M^{-1} ($\Delta H = -6.9$ kcal mol^{-1} and $T\Delta S = 2.8$ kcal mol^{-1}) for the **1·2** complex. However, the integrated data display an increasing amount of heat evolved per injection up to approximately 0.9 equiv of DAN, which compromises the goodness of fit.

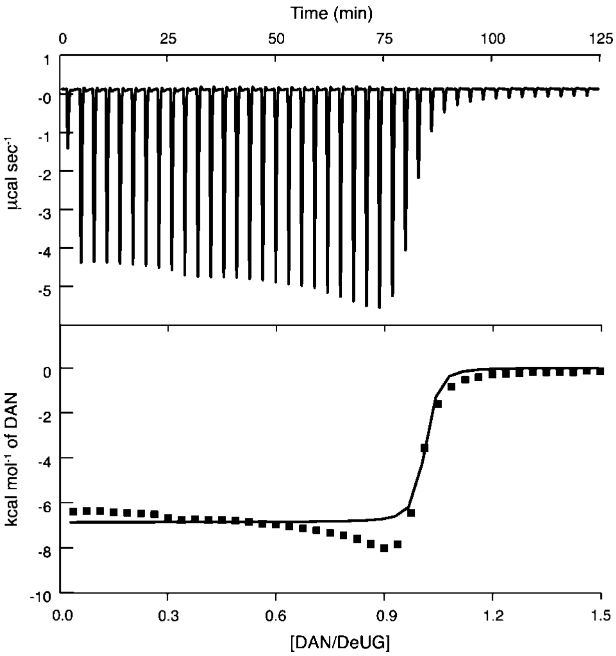

Figure 2. ITC of DeUG·DAN in $CHCl_3$ showing the enthalpic attenuation due to dissociation of the DeUG dimer.

It was hypothesized that this apparent anomaly arose from an enthalpic attenuation caused by the endothermic cost of dissociating the DeUG homocomplex. Specifically, heterocomplexation of DeUG during the titration shifts the DeUG self-association equilibrium toward free DeUG. In this case, the total enthalpy measured for any single injection (up to 1:1 stoichiometry) is the sum of the endothermic homocomplex dissociation and the exothermic heterocomplex association. As the titration approaches 1:1 stoichiometry, the DeUG self-association equilibrium is being driven toward a larger fraction of dissociated species. Thus, the enthalpic attenuation diminishes with each successive injection, leading to the observed slope in the initial portion of the isotherm.

The difference between the enthalpy for the first injection and the most exothermic injection (at ca. 0.9 equiv) should closely correspond to the enthalpy of self-association for DeUG. Moreover, an analysis of the concentration of each species through the titration experiment should reveal that the DeUG dimer−monomer equilibrium is being perturbed as proposed. Indeed, a plot of these concentrations reveals that this is the case (see Supporting Information). The ΔH for DeUG self-association as determined by ITC in this manner was −1.6 kcal mol^{-1}. The ΔH value independently

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[13] (a) Connors, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley-Interscience: New York, 1987. (b) Hirose, K. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *39*, 193–209.

determined by a ^{1}H NMR van't Hoff experiment is in good agreement with that determined by ITC, giving -1.7 kcal mol^{-1} (see Supporting Information). Thus, the DeUG·DAN K_{assoc} value can be estimated to be 1.9×10^8 M^{-1} by correcting the ΔH in this manner.

An ITC experiment was performed in 5% DMSO/$CHCl_3$, a more competitive solvent that was expected to reduce the contribution of DeUG self-association and diminish the enthalpic attentuation. From titrations of DAN into DeUG at 25 °C in this solvent mixture, the best fit curve gave $K_{\mathrm{assoc}} = 2.1 \times 10^4$ M^{-1} ($\Delta H = -3.1$ kcal mol^{-1} and $T\Delta S = 2.8$ kcal mol^{-1}), and the isotherm did not display any enthalpic anomalies (see Supporting Information). This association constant is within the previously reported range.[7]

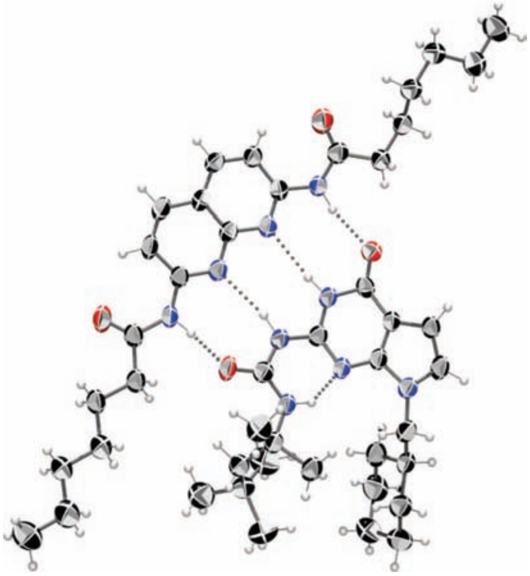

Figure 3. ORTEP representation of a DeUG·DAN heterocomplex. Thermal ellipsoids represent 50% probability.

Repeated attempts to obtain crystals suitable for X-ray analysis of the **1**·**2** heterocomplex proved unsuccessful. However, using the previously reported 1,1,3,3-tetra-methylbutyl urea DeUG analogue,[7] triclinic crystals of a DeUG·DAN heterocomplex suitable for X-ray analysis were obtained via slow evaporation from chloroform (Figure 3). Although there are several reports of solid-state structures of quadruply hydrogen-bonded dimers,[4,14] to our knowledge, this is the first report of a solid-state structure of a quadruply hydrogen-bonded heterocomplex formed from a contiguous array of hydrogen bonds.[15] Some disorder in one of the heptanoyl chains of DAN was observed. The two molecules are nearly coplanar with an angle of 9.8° between the average heterocycle planes with the amide-urea N−H···O hydrogen-bond length being 1.79(8) Å (angle, 173°), the urea-napthyridine N−H···N hydrogen-bond length being 2.18(1) Å (angle, 165°), the lactam-naphthyridine N−H···N hydrogen-bond length being 2.17(3) Å (angle, 169°), and the amide-lactam N−H···O hydrogen-bond length being 1.91(3) Å (angle, 166°). In the heterocomplex, the intramolecular hydrogen bond in DeUG was found to be 1.90(0) Å (angle, 143°).

In conclusion, we have demonstrated a convenient, scalable, and high-yielding synthesis of DeUG analogues. The synthesis provides the ability to functionalize the module with a variety of functional groups via straightforward transformations. A combination of ^{1}H NMR, ITC, van't Hoff analysis, and X-ray analyses were used to characterize both DeUG's self-association and its complexation with DAN. Supramolecular polymers and surface self-assembly studies using these new DeUG variants are currently being investigated and will be reported in due course.

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Supporting Information Available: General and detailed experimental procedures, X-ray analyses data in CIF format, and ^{1}H NMR spectra for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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(14) Selected examples: (a) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761–6769. (b) Gong, B.; Yan, Y.; Zeng, H.; Skrzypczak-Jankunn, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607–5608. (c) Goswami, S.; Dey, S.; Gallagher, J. F.; Lough, A. J.; García-Granada, S.; Torre-Fernández, L.; Alkorta, I.; Elguero, J. *J. Mol. Struct.* **2007**, *846*, 97–107.

(15) For an example invoking a C-H···O interaction as the fourth hydrogen bond, see: Quinn, J. R.; Zimmerman, S. C. *Org. Lett.* **2004**, *6*, 1649–1652.