ORGANIC LETTERS

2006
Vol. 8, No. 8
1589−1592

Higher Affinity Quadruply Hydrogen-Bonded Complexation with 7-Deazaguanine Urea

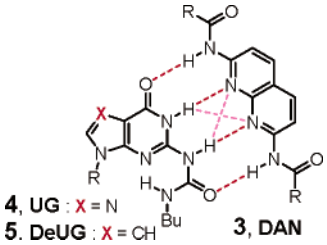
Hugo C. Ong and Steven C. Zimmerman*

Department of Chemistry, 600 South Mathews Avenue, University of Illinois, Urbana, Illinios 61801

sczimmer@uiuc.edu

Received January 22, 2006

ABSTRACT



UG forms a highly stable quadruply hydrogen-bonded heterocomplex with DAN, but the fidelity of the complex is lowered somewhat by the Hoogsteen-side oligomerization of UG ($K_{assoc} \sim 230$ M^{-1}, $CDCl_3$). DeUG was prepared as a more robust analogue of UG lacking the Hoogsteen nitrogen atom. Remarkably, the deaza analogue, DeUG, forms a much more stable complex with DAN (>10-fold higher K_{assoc} for DeUG·DAN vs UG·DAN) but also dimerizes more strongly ($K_{dim} = 880 \pm 40$ M^{-1}, $CDCl_3$) by adopting a conformation preorganized for both binding and dimerization.

Recent efforts to expand the "supramolecular toolkit" have focused on hydrogen-bonded complexes of tunable strength in organic solvents.[1] The *quadruply hydrogen-bonded* complexes, in particular, are an attractive class as a result of their high binding strengths and synthetic accessibility. Our DeAP unit (**1**)[2] and the Meijer−Sijbesma UPy unit (**2**)[3] are examples that dimerize strongly via AADD motifs (Figure 1). Both units also adopt an ADDA form (**1′** and **2′**) that very tightly binds 2,7-diamido-1,8-naphthyridine (DAN, **3**).[2,4] Because **1** and **2** can present strongly self-associating AADD hydrogen bonding arrays, the overall *fidelity* with which they complex with **3** is lowered.[5] We showed that in comparison to **1** and **2**, the AADD form of the UG unit **4** is much higher in energy than the ADDA form so it complexes **3** with a much higher fidelity. Thus, **4** tightly complexed **3** ($K_{assoc} \sim 5 \times 10^7$ M^{-1}, $CHCl_3$) via form **4′** but did not dimerize strongly via form **4′′**.[6] The UG·DAN complex is well optimized; however, two aspects of the UG unit make it less than an ideal subunit. First, the UG weakly self-associates ($K_{assoc} \sim 230$ M^{-1}) via oligomerization of form **4**,[6] the urea group hydrogen bonding at the Hoogsteen side of the UG

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

(2) (a) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710−9711. (b) Corbin, P. S.; Lawless, L. J.; Li, Z.-T.; Ma, Y.; Witmer, M. J.; Zimmerman, S. C. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 5099−5104.

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

(4) (a) Wang, X.-Z.; Li, X.-Q.; Shao, X.-B.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T.; Chen, Y.-Q. *Chem. Eur. J.* **2003**, *9*, 2904−2913. (b) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 810−811.

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

(6) (a) Park, T.; Zimmerman, S. C.; Nakashima, S. *J. Am. Chem. Soc.* **2005**, *127*, 6520−6521. (b) Park, T.; Todd, E. M.; Nakashima, S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2005**, *127*, 18133−18142.

10.1021/ol0601803 CCC: $33.50
Published on Web 03/25/2006

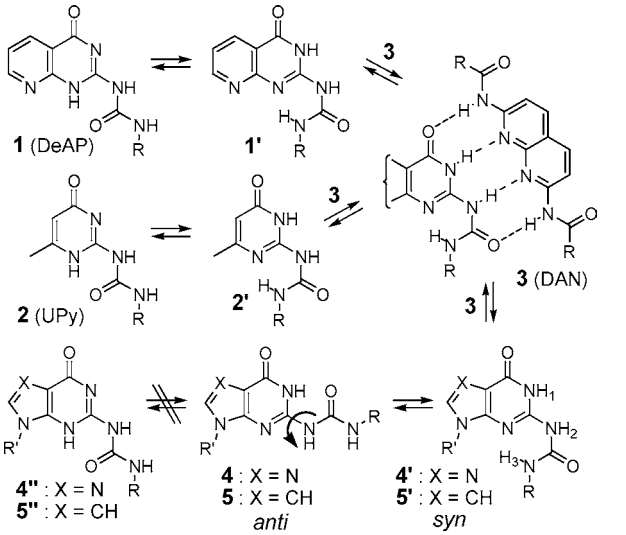


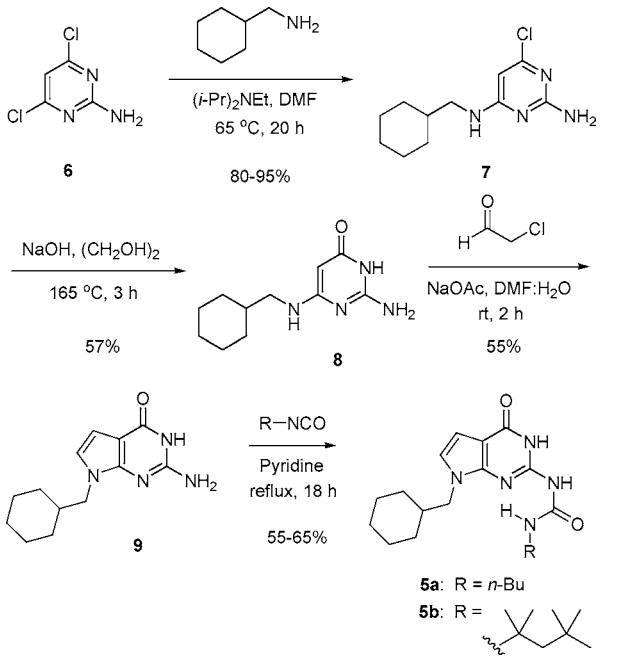
Figure 1. Various tautomers/conformers of DeAP **1**, UPy **2**, UG **4**, and DeUG **5** and complexes of **1′**, **2′**, **4′**, and **5′** with DAN (**3**). In **1** and **2**, R = Bu. In **3**, R = C_6H_{13}, and in **4** R = Bu, R′ = 2′,3′,5′-*O*-acetylribose. See Scheme 1 for R in **5**.

unit. Additionally, the ribose unit is large, and its labile linkage to the base limits its utility in some applications. Herein, we describe the preparation and study of the ureido-7-deazaguanine (DeUG) **5**, an analogue of UG which lacks both the ribose unit and the Hoogsteen-side nitrogen atom *N*(7), thought to be essential for the oligomerization.

Various 7-deazaguanines were reported as replacements for guanine in DNA and as enzyme inhibitors.[7] The reported synthesis was adapted to the synthesis of DeUG **3**[8] which began with the amination of 2-amino-4,6-dichloropyrimidine (**6**). Although **6** can be obtained by commercial means, it is more cheaply obtained by synthesis from 2-amino-4,6-dihydroxypyrimidine in $POCl_3$ and *N*,*N*-dimethylaniline, which occurs in near quantitative yield (not shown).[9] The amination with cyclohexylmethylamine occurred smoothly in DMF with Hünig's base to give **7** in good yields (80−95%). The cyclohexylmethyl group was chosen to provide organic solubility. Basic hydrolysis in ethylene glycol under reflux gave **8** in 57% yield. Treatment of the pyrimidinone with α-chloroacetaldehyde in a DMF/H_2O mixture with NaOAc gave the 7-deazaguanine derivative **9** in 55% yield. We previously found the amino group of guanine and pterin derivatives to be quite unreactive;[2,5] however, the desired ureido moiety in **5a** could be prepared by treatment of **9** with 2.2 equiv of *n*-BuNCO in refluxing pyridine in 65% yield. For added solubility, **5b** was also prepared using the corresponding isocyanate (6 equiv) in 55% yield. No chromatography was required until the installment of the ureido group in the final step, allowing for a preparation that could be readily performed on multigram scale.

In UG, the *anti* form (Figure 1) was dominant in all solvents and concentrations examined. However, the strong complexation of DAN indicated that the *syn* form was energetically accessible. Unexpectedly, ^{1}H NMR studies of the conformation of DeUG **5a** and **5b** showed its conformation to be solvent dependent. In DMSO-d_6 at 5 mM **5b**, the *anti* form is dominant; at the same concentration in $CDCl_3$, the NH(3) proton moves downfield by 1.71 ppm to 8.94 ppm, in contrast to NH(1) and NH(2) which move upfield (see the Supporting Information). The large downfield shift can be rationalized by the intramolecular hydrogen bond that is formed in the *syn* conformation. The NH(3) peak also broadens, which we have found to be characteristic of intramolecularly hydrogen-bonded pyridyl and naphthyridinyl ureas.[2] Further evidence for this tautomeric form[10] and

Scheme 1



conformation in chloroform came from an NOE study, summarized in Figure 2. Upon irradiation of NH(3) of **5b**, a key NOE was observed to the methylene of the cyclohexylmethyl group (H_a). No such signal was observed when either NH(1) or NH(2) was irradiated. These results suggest that DeUG does not oligomerize in the same manner as UG. In fact, DeUG can only self-associate through dimerization via the *syn* form, which we find to be consistent with our observations in $CDCl_3$. The lactim (enol) tautomer of **5b** could not be ruled out by the NMR data. However, a similar

(7) (a) Fletcher, T. M.; Cathers, B. E.; Ravikumar K. S.; Mamiya, B. M.; Kerwin, S. M. *Bioorg. Chem.* **2001**, *29*, 36−55. (b) Gangjee, A.; Dubash, N. P.; Kisliuk, R. L. *J. Heterocycl. Chem.* **2001**, *38*, 349−354. (c) Gibson, C. L.; Rosa, S. L.; Ohta, K.; Boyle, P. H.; Leurquin, F.; Lemaçon, A.; Suckling, C. J. *Tetrahedron* **2004**, *60*, 943−959.

(8) Park, T.; Mayer, M. F.; Nakashima, S.; Zimmerman, S. C. *Synlett*. **2005**, *9*, 1435−1436.

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

(10) DeUG **5b** showed small amounts of another tautomer (<3% by NMR integration) which appeared to dimerize strongly in $CDCl_3$. The identity of this tautomer was not determined (see the Supporting Information), and it was not observed with **5a**.

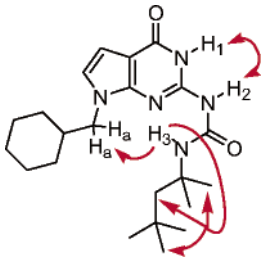


Figure 2. Key NOE contacts observed for **5b** (DeUG).

tautomer formed by UPy was shown by Meijer, Sijbesma, and co-workers[11] to very tightly dimerize ($K_{dim} > 4.5 \times 10^5$ M^{-1}) by its self-complementary DADA hydrogen bonding array, and this is inconsistent with the self-association study described below.

The self-association of DeUG was examined by NMR. A dilution study with **5b** was performed in $CDCl_3$ from 50 μM to 15 mM at 20 °C; the signal for NH(1) was followed throughout the study, and the data was fit to a nonlinear binding equation to provide a K_{dim} of 880 ± 40 M^{-1} (Figure 3). The signals for NH(2) and -(3) could not be followed

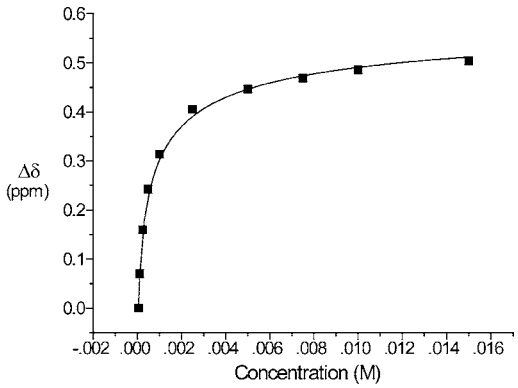


Figure 3. Representative plot of $\Delta\delta$ vs [DeUG, **5b**] for the dilution study in $CDCl_3$ at 20 °C. Data for this proton was fit to a nonlinear binding equation to calculate K_{dim}.

due to poorly resolved signals at 50 μM. It should be noted that, by virtue of it possessing a symmetric (palindromic) ADDA hydrogen-bonding pattern, in principle, there are four ways in which DeUG may self-associate. However, given that pyridone dimers tend to be more stable than urea dimers ($K_{dim} = 50-100$ M^{-1} vs $K_{dim} = 5-15$ M^{-1}, respectively),[12] it is likely that the lactam dimer and the lactam/urea dimers contribute more than the urea dimer.

The upfield shift of the key NH signals upon dilution indicates that DeUG does not form strong UPy- or DeAP-type dimers via $(AADD)_2$ or $(ADAD)_2$ motifs.[2,3,11] Furthermore, DeUG does not oligomerize by the Hoogsteen-side hydrogen bonding exhibited by UG. However, the removal of the 7-aza group unexpectedly causes an equilibrium shift from the *anti*-form **5** to the *syn*-form **5′**. This conformer is able to dimerize somewhat more strongly by virtue of its pyridone-type moiety. The origin of this conformation shift is not readily apparent. However, computational studies indicate the two forms to be close in energy so that small structural, electronic, or environmental changes can readily effect the equilibrium.

A 1:1 mixture of **5** (**a** and **b**, in separate experiments) and **3** in $CDCl_3$ showed large downfield shifts of the NH protons relative to the free components: NH(1), NH(2), and NH(3) moved by 2.0, 1.8, and 0.6 ppm, respectively. The relatively small shift exhibited by NH(3) is consistent with the *syn* model in which it is intramolecularly hydrogen-bonded, and not directly involved with heterocomplexation. No new peaks were observed nor did any shift occur in the DeUG unit upon dilution from 10 mM to 10 μM (see the Supporting Information). Thus, assuming 95% complexation, a lower limit of $K_{assoc} > 10^7$ M^{-1} can be estimated.

The shift in equilibrium from the *anti*- to *syn*-conformation means **5** should be better preorganized for binding DAN (**3**). Because of the difficulty in accurately determining such high binding constants in $CDCl_3$, a direct competition experiment was performed. Thus, DAN was titrated into an equimolar solution of DeUG and UG in $CDCl_3$ (see Figure 4 and the Supporting Information). As the concentration of DAN was increased, the DeUG·DAN complex appeared to form preferentially over the UG·DAN complex. This observation

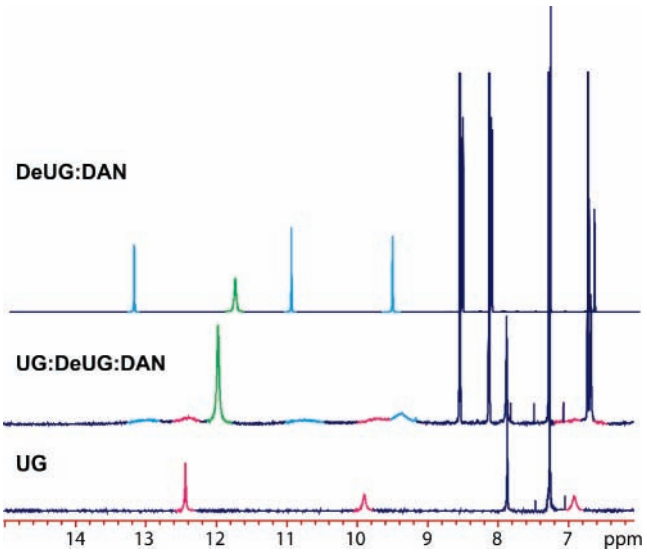


Figure 4. Stacked NMR plots of 1:1 DeUG·DAN, **5b·3** (top), 1:1:1 UG·DeUG·DAN (middle), and UG (bottom). Each module is at 10 mM concentration in $CDCl_3$ at 20 °C. The DeUG peaks are shown in blue, DAN in green, and UG in pink. Top of $CHCl_3$ peak cut off.

(11) Beijer, F. H.; Sijbesma, R. P.; Koojiman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761−6769.

(12) (a) Hammes, G. G.; Park, A. C. *J. Am. Chem. Soc.* **1969**, *91*, 956−961. (b) Gallant, M.; Viet, M. T. P.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 721−723. (c) Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215−2217. (d) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475−10488.

is particularly evident in Figure 4 where a 1:1:1 mixture of UG·DeUG·DAN (i.e., **4**·**5b**·**3**) exhibits a ^{1}H NMR spectrum in $CDCl_3$ that, with the exception of broadening and some slight shifts, appears to be a composite of the spectrum of UG (**4**) and the DeUG·DAN (**5b**·**3**) complex. It was not until an excess of 1.0 equiv of DAN was added that the UG·DAN complex could be observed.

The binding strengths were also compared directly by employing a more competitive solvent, namely 5% DMSO-d_6/$CDCl_3$. Titration experiments showed that UG (**4**) binds DAN (**3**) with $K_{assoc} = 3200\ M^{-1}$ in this solvent.[13] This binding strength is comparable to DeAP·DAN (**1**·**3**), which we have previously determined to be $K_{assoc} = 3030\ M^{-1}$.[2] The DeUG·DAN (**5b**·**3**) complex, however, gave a binding constant of $K_{assoc} \approx 10^4-10^5\ M^{-1}$. Only an approximate value could be obtained for this complex, due to extreme broadening of the −NH peaks at <1.0 equiv of DAN. However, the titration curve clearly indicates a stronger complex (see the Supporting Information); even at 1.0 equiv of DAN at micromolar concentrations, the NH(1) proton quickly reaches 65% of its maximum chemical shift change. Taken together with the competition experiments, we conclude that the DeUG·DAN complex is indeed stronger than UG·DAN, perhaps >10-fold higher.

In conclusion, we have developed a UG analogue, DeUG, which lacks the large, labile ribose unit yet forms highly stable, quadruply hydrogen-bonded complexes with DAN. The deazaguanine unit lacking N(7) did prevent Hoogsteen-side oligomerization. However, unexpectedly, the urea group of DeUG (**5**) adopts the *syn*-form whereas the urea in UG (**4**) was exclusively in the *anti*-form. The *syn* conformer is preorganized for binding, but also stronger dimerization via the pyridone-type moiety. Thus, the DeUG unit dimerization constant is about 3−4 times than that for UG but it complexes DAN with a K_{assoc} that is ≥10-fold tighter. The net effect is that DeUG is an overall better choice as a complement for DAN, except in cases where it will be used in excess. In such cases, the stronger dimerization of DeUG will lead to a lowered fidelity in the overall assembly. Efforts are currently directed toward developing DeUG analogues for applications in nanotechnology and supramolecular polymer chemistry.

(13) Park, T. Unpublished results.

Acknowledgment. We thank the ICI National Starch and Chemical Company and the U.S. Department of Energy, Division of Materials Science, under Award No. DEFG02-91ER45439 through the Frederick Seitz Materials Research Laboratory at the University of Illinois at Urbana−Champaign, for funding this work. Taiho Park and Darrell Kuykendall are gratefully acknowledged for their synthetic contributions. Eric Todd is also acknowledged for his work on examining the fidelity of DeUG.

Supporting Information Available: Detailed descriptions of all experimental procedures along with characterization data and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0601803