Design, Synthesis, and Self-Assembly of "Artificial Dinucleotide Duplexes"

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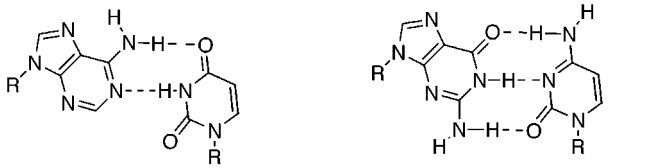
The synthesis of the A−U and G−C functionalized systems **1**, **2**, **3**, and **4** has been accomplished using palladium-mediated cross-coupling reactions. These systems undergo self-association in nonpolar solvents such as $CDCl_3$ as judged from FABMS and NMR spectroscopic analyses.

Introduction

The specific hydrogen-bonding interactions that occur between complementary DNA bases provide a time-honored affirmation of how appropriately designed functionality may be used to induce spontaneous assembly in complex supramolecules. Indeed, the efficiency and apparent simplicity whereby information is stored and transferred in natural nucleic acids has inspired us[1] and others[2−4] to reproduce the essential features of duplex DNA using much simpler synthetic systems. Although many self-complementary structures capable of undergoing assembly have been synthesized of late,[2,3] only a few synthetic systems are known that employ DNA-like complementary purine−pyrimidine base pairing (Chart 1) as the critical recognition motif.[1,4] This seeming unpopularity could reflect the fact that (1) the binding affinities associated with adenosine(A)−thymidine(T) [or uridine(U)] "dimerization" are too low ($K_a \approx 10^2$ M^{-1} in $CDCl_3$[5]) and (2) cytidine(C) and guanosine(G), which do have high affinities for complementary association ($K_a \approx 10^4$ M^{-1} in $CHCl_3$[4e,f,6]), are highly insoluble in organic media and thus constitute species with which it is difficult to work. Despite these potential difficulties, we remain of the opinion that the continued study of nucleic acid base derived systems is worthwhile; it could help us to understand better the details of base pairing under abiotic conditions and, perhaps, provide a means of constructing complex, but well-defined synthetic arrays. In this paper we discuss systems that are capable of undergoing self-dimerization in accord with the generalized equilibrium shown in Scheme 1. We recently reported, in Communication form,[7] the synthesis and self-assembling properties of **I**. In this paper we provide full synthetic details for the mononuclear constituents of **I** (from compound **1**) and also report the synthesis and solution-phase self-assembly properties of analogous ensembles, namely, **II** (from **2**), **III** (from **3**), and **IV** (from **4**) (Chart 2).

Chart 1



Results and Discussion

Molecular Design. The basic principles underlying the design of the self-complementary systems **1**−**4** are rigidity and solubility. The first of these design characteristic is deemed essential since conformational flexibility carries with it a large entropic "penalty" that must be paid during the course of the self-assembly process. Such a "payment" weakens the stability of the resulting complexes and can also preclude entirely the formation of the sought-after duplexlike dimer in the absence of some further stabilizing interaction.[4a−d,i] The need for solubility is even more straightforward. For a self-dimerizing system to work, it must be rendered soluble in a solvent where the putative hydrogen-bonding inter-

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Scheme 1

actions are appreciable. In practice, this means making the target systems soluble in $CHCl_3$ or similar solvents that do not compete effectively for H-bond donor or acceptor sites.

On the basis of an appreciation that rigidity and solubility are critical, four initial target molecules **1**−**4** were chosen. These targets, designed to form self-complementary duplexes, are similar in the general sense that all of them combine the following features: (1) complementary molecular recognition motifs involving either adenosine/uridine or guanosine/cytidine base-pairing subunits; (2) rigid aromatic spacer and an easy-to-incorporate acetylene linker; (3) protecting groups on the ribose subunits that render the target molecules soluble in organic media.

Notwithstanding the similarities mentioned above, these systems are structurally different. For instance, **1** differs from **4** in both the size of the protecting groups and the number of hydrogen bonds; **2** differs from **1** and **4** in the size of the protecting groups and the number of hydrogen bonds, respectively; and the only difference between **1** and **3** is the degree of preorganization. Thus, the study of these systems, it was expected, would not only allow the effects of molecular rigidity to be evaluated in terms of the effect such factors could have on aggregation behavior but also allow those associated with seemingly minor variations in structure (e.g., number of hydrogen bonds[8]) to be considered in a similar light.

Synthesis of the Precursors to Ensembles I, II, III, and IV. As mentioned earlier, all the monomeric targets (i.e., **1**−**4**) needed to prepare ensembles **1**−**IV** contain an acetylene linker. This structural motif serves two functions: it provides both structural rigidity and abets synthetic accessibility. Fortunately, this type of linkage can now be introduced into many systems, including monomers **1**−**4**, as the result of palladium-mediated cross-coupling chemistry.[9−11] As it relates here, this chemistry is summarized in Schemes 2−6. It is also discussed explicitly below.

The synthesis of 1,8-diethynylanthracene (**5**) from 1,8-dichloroanthracene[12] was described previously.[13] 5-Iodouridines (**6a**) and 8-bromoadenosines (**9a**) were synthesized according to the reported procedures.[14] With these intermediates in hand, the key C−C bond formation steps of target molecule **1** (i.e., the palladium-catalyzed cross-coupling reactions) could be attempted. Scheme 2 summarizes the relevant chemistry. The first palladium-catalyzed cross-coupling reaction involves a coupling between 1,8-diethynylanthracene **5** and 5-iodouridine **6a**. This reaction, carried out at room temperature under argon, gives a mixture of both mono- and bis-uridine- substituted anthracenes **7a** and **8a**. The ratio of these two products depends largely on the ratio of the two starting materials used. For instance, a 1:1 molar ratio of **5**/**6a** gave a significant amount of the bis-substituted compound **8a** (>50%). While this material could be useful as a control compound, it was not the desired product in this particular synthesis. Fortunately, it was found, after considerable experimentation, that using a 3:1 molar ratio of **5**/**6a** would give the mono-uridine- substituted anthracene **7a** as the major product (89% yield based on **6a**). The alkyne functional group in **7a** could then be coupled with 8-bromoadenosine **9a** under conditions similar to those used in the first coupling reaction (with the exception that a higher temperature (60 °C) was necessary to complete the transformation). Using this approach, the target compound **1** was obtained in 71% yield after chromatographic purification.

The same sequence of reactions was also used to synthesize target molecule **2** (Scheme 2) from **6b** and **9b**[15] in 45% overall yield.

Surprisingly and in contrast to what was true for the syntheses of the analogous compounds **7a** and **7b**, the reaction between 5-iodouridine **6a** and 4,6-diethynyldibenzofuran **11** (Scheme 3), which was prepared in 88% overall yield from 4,6-diiododibenzofuran **10**,[16] gave rise to only a very low yield (5%) of mono-uridine-substituted dibenzofuran **12** (i.e., the key intermediate in the synthesis of target monomer **3**). Instead, the bis-uridine-substituted compound **13** was found to be the major product (>90%), regardless of the bis-alkyne **11** to iodouridine **6a** ratio employed. An alternative route was thus explored. Here, the basic idea was to switch the functional groups on the two reactants in an attempt to reduce their reactivity[9] to the point where the reaction would stop at the monosubstitution stage. In fact, as summarized in Scheme 4, this approach worked well when 5-ethynyluridine **14** was used as one reactant and diiododibenzofuran **10** was used as the other.

As illustrated in Scheme 4, four successive palladium-mediated couplings were needed to assemble the basic skeleton of monomer **3**. The first of these couplings produced 5-ethynyluridine **15**; it was obtained in 78% overall yield from the reaction of 5-iodouridine **6a** with TMS-acetylene followed by a removal of the TMS group with TBAF (to give **15**). The second coupling reaction involved the use of this precursor (**15**) and 4,6-diiododibenzofuran **10**. This gave rise to a mixture of mono- and bis-uridine-substituted products (compounds **16** and **13**, respectively). Here, in analogy to what was observed earlier, the relative ratio of the resulting products was found to depend on the relative ratio of the two starting materials employed. This meant that, after optimization of the reaction conditions, the mono iodo-substituted dibenzofuran **16** could be obtained in 87% yield. The same palladiun-mediated coupling sequence used to prepare **15** was applied to this latter intermediate (i.e.,

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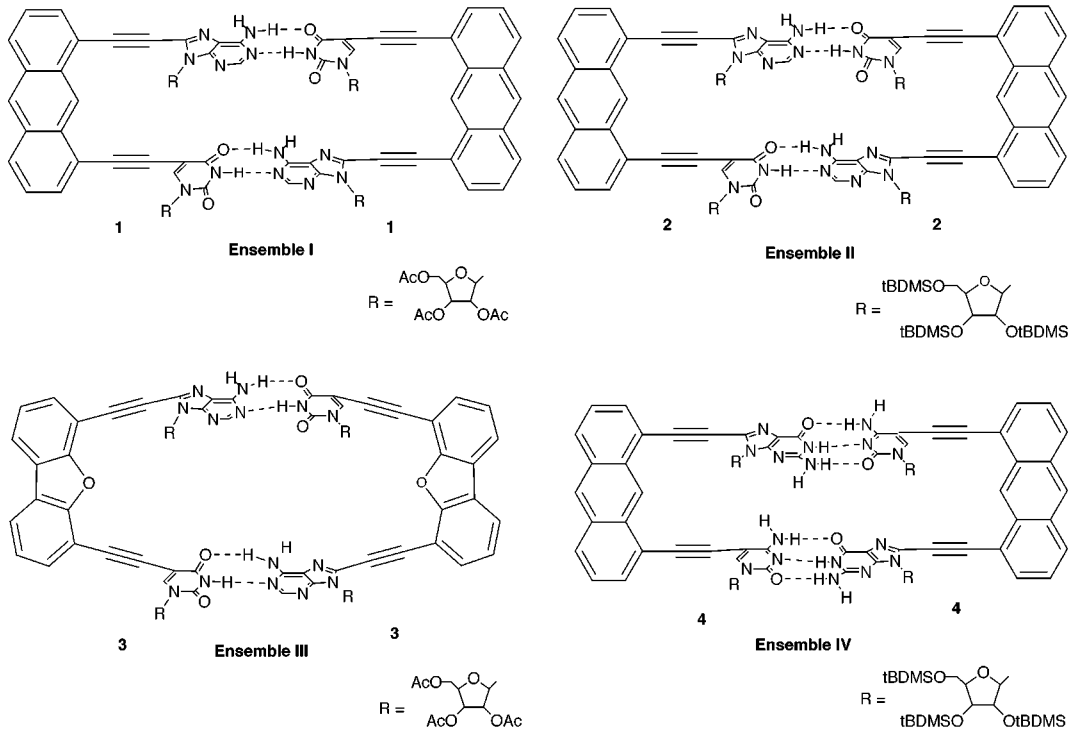
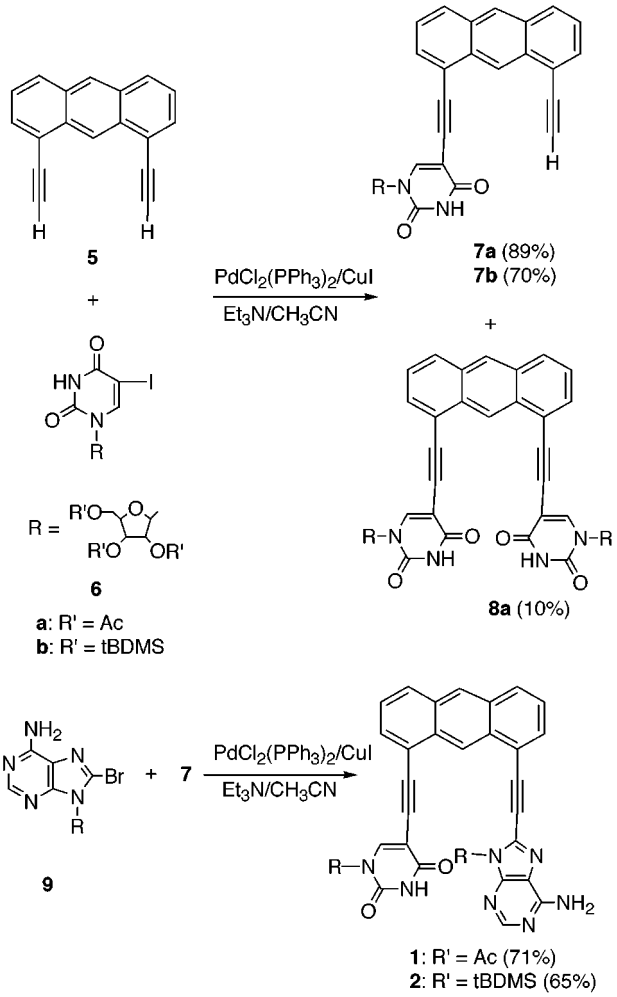
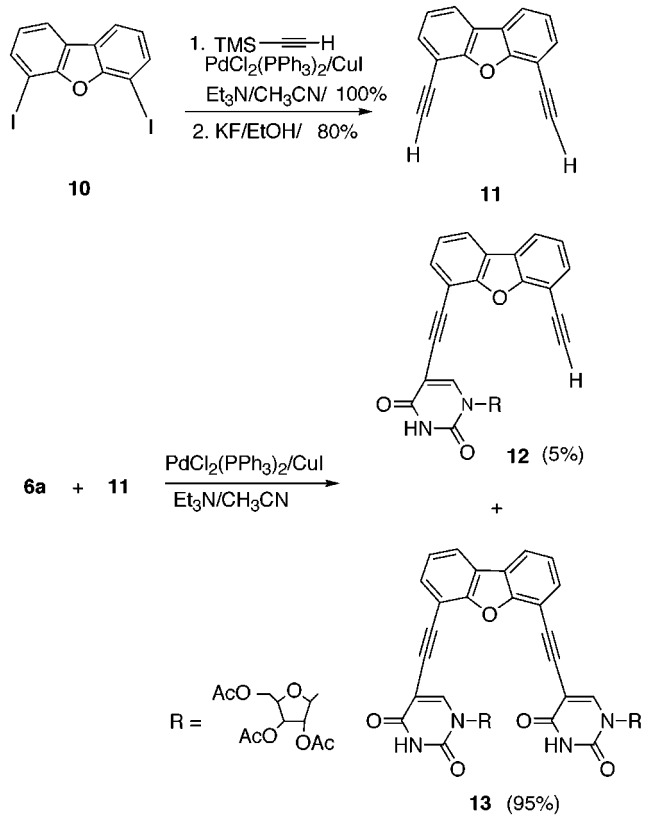
Chart 2



Scheme 2



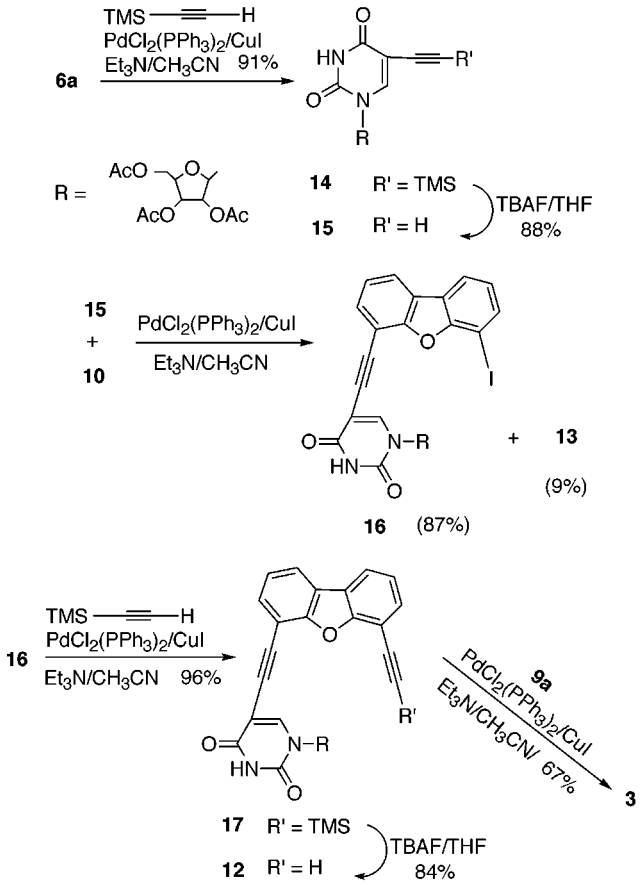
Scheme 3



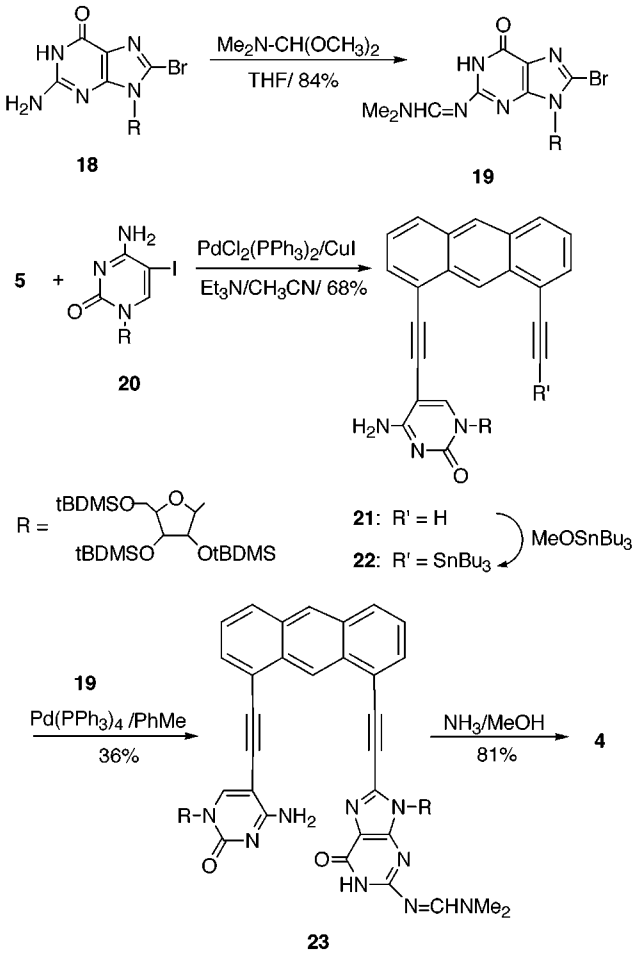
16) to give the mono-uridine-substituted compound **12** in 80% overall yield. The alkyne functional group present in **12** could then be coupled with the 8-bromoadenosine **9a** at 60 °C to give the desired target monomer **3** in 67% yield after chromatographic purification.

The synthesis of the G/C analogue **4** proved to be a much more demanding task. Besides containing protecting groups that are different than those found in other targets, such as **3**, this system also contains a guanosine functionality. These two aspects complicated the syn-

Scheme 4



Scheme 5



thesis. After considerable experimentation, it was found that the alkyne functional groups on the anthracene had to be activated by forming the corresponding organostannyl derivatives.[17] Additionally, it was found that the amino group of the guanosine derivative **18** had to be protected. Fortunately the *N*,*N*-dimethylformamidine functionality was found suitable for this purpose. The synthetic sequence that resulted from these changes is shown in Scheme 5. In terms of specifics, the amino group of guanosine **18** was protected with *N*,*N*-dimethylformamidine in 84% yield by reacting with excess *N*,*N*-dimethylformamide dimethyl acetal in anhydrous THF. The coupling reaction between **5** and **20**[18] produced the desired mono-cytidine-substituted compound **21** in good yield (68%). The alkyne functional group of **21** was converted to its organostannyl derivative **22** by being heated in toluene at reflux in the presence of excess tributyltin methoxide, a species that, in turn, was synthesized from bis(tributyltin)oxide and dimethyl carbonate.[19] The resulting organostannyl product **22** proved to be unstable to column chromatographic purification. Therefore, it was prepared and used in situ. This was practical since toluene was the solvent used in both reactions. Thus, a mixture of **19**, **21**, and tributyltin methoxide was heated in toluene at reflux for 10 h in the presence of $Pd(PPh_3)_4$ to give rise to **23** in 36% yield after chromatographic purification. Finally, the amino protecting group of compound **23** was removed by treatment with saturated methanolic ammonia at room temperature overnight. This gave target **4** in 81% yield after silica gel column chromatographic purification.

An alternative approach to target molecule **4** was also investigated. It is summarized in Scheme 6. In this case, the starting materials are the bis-alkyne **5**, tributyltin methoxide, and 1 equiv of the 8-bromoguanosine derivative **19**. After these materials were mixed together in toluene and $PdCl_2(PPh_3)_2$ added, the reaction was made to proceed by being heated at reflux for 10 h. This gave the mono-guanosine-substituted compound **25** in 52% yield after silica gel column chromatographic purification. Subsequent coupling of the resulting intermediate product, **25**, with 5-iodocytidine (**20**) gave compound **23** in 71% yield after column chromatographic purification. Target **4** was then obtained in its final deprotected form by being treated with ammonia in methanol.

Self-Assembly of I, II, III, and IV. As stated before, the primary goal of the work is to understand various factors which influence the self-assembly of duplexes via base pairing. Thus, once the synthesis of the target monomers was complete, the next task was to find out whether these presumed-to-be self-complementary compounds would in fact self-assemble to form the expected corresponding duplexes, namely, structures **I**,[7] **II**, **III**, and **IV**. Here, the goals were to determine how structural variations such as the size of protecting groups, degree of preorganization, and number of hydrogen bond donors and acceptors in the monomers would affect the stability and architecture of the resulting complexes. These issues

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Scheme 6

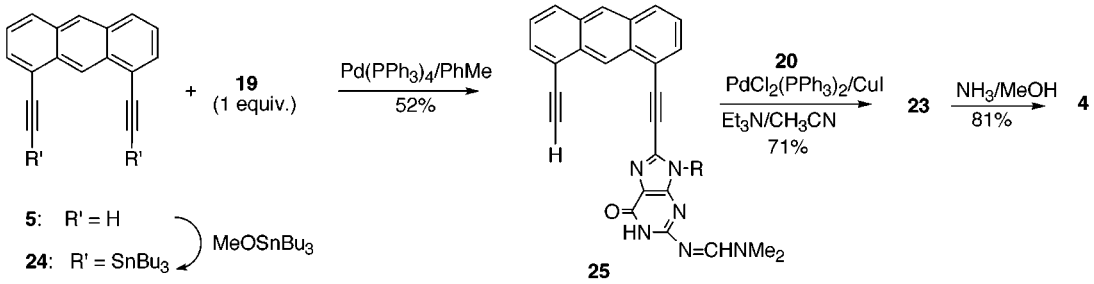

Table 1. FABMS Characterization of Ensembles I, II, III, and IV

observed peak	found	composition	calculation
I	1970.5520	$C_{98}H_{86}N_{14}O_{32}$	1970.5533
II + 1	2836.4712	$C_{146}H_{231}N_{14}O_{20}Si_{12}$	2836.4721
III + 1	1951.5210	$C_{94}H_{83}N_{14}O_{34}$	1951.5196
IV + 1	2866.4900	$C_{146}H_{233}N_{16}O_{20}Si_{12}$	2866.4939

were explored using mass spectrometric, vapor pressure osmometric (VPO), and NMR spectroscopic analyses.

Mass Spectrometry. Initial evidence that stable self-assembled complexes **I**, **II**, **III**, and **IV** could be formed from the monomeric precursors **1**, **2**, **3**, and **4** came from fast atom bombardment mass spectrometric (FAB-MS) experiments. Both peaks corresponding to the individual monomeric components and peaks attributable to their dimeric complexes (i.e., **I**, **II**, **III**, and **IV**, respectively) were observed. On the other hand, control experiments conducted under the same conditions using mixtures of **7a** /**9a**, **9a**/**13**, and **1**/**4** did not give the corresponding noncovalent dimeric peaks. This indicates that the observed noncovalent dimeric species were formed as the result of complementary base-pair interactions.

Interestingly, when a 1/1 mixture of compounds **1** and **3** was measured using the same conditions, a new peak at *m*/*z* 1962 in addition to those expected for **I** and **III** was observed. This peak most likely belongs to the mismatched heterodimeric species between **1** and **3**. This result was not surprising since the two compounds are functionally complementary to each other. This type of mismatched phenomenon was also observed by Rebek et al.[20] High-resolution mass spectrometric analysis of these dimeric signals proved to be consistent with their proposed chemical formulas. The results are summarized in Table 1.

VPO Experiments. The average molecular weights of **I** and **III** were also determined in solution using vapor pressure osmometry (VPO) using 1, 2-dichloroethane as the solvent and compound **13** as the molecular weight standard. From these measurements, a M_w value of 2210 ± 45 (from three independent measurements) was obtained for **I**. This value is in agreement with the molecular weight of dimer **I** containing two trapped or bound dichloroethane molecules (M_w = 2168). In contrast, the VPO measurements for system **3** gave a value of 1190 ± 30, which is close to the molecular weight of the monomeric species (M_w = 950). Taken together, these results provide an indication that **I** is a more tightly bound complex than **III**.

Result from Elemental Analysis. The VPO experiments are consistent with a scenario wherein compound **1** self-associates to form a tightly bonded duplex **I** and does so in a way such that two solvent molecules are associated with the duplex. This interpretation was further supported by elemental analyses. For instance, when compound **1** was recrystallized from 1,2-dichloroethane, the following elemental analysis was obtained: C, 56.51; H, 4.43; N, 8.94; Cl, 6.59. The calculated values for bis-1,2-dichloroethane adduct of **I** $(C_{49}H_{43}N_7O_{16})_2\cdot(C_2H_4Cl_2)_2$ are as follows: C, 56.5; H, 4.37; N, 9.05; Cl, 6.46. Recrystallization of compound **1** from a mixture of benzene and dichloromethane, on the other hand, produced these microanalysis values: C, 62.07; H, 4.65; N, 9.17. This corresponds to dimeric species **I** that either incorporates two benzene molecules within its boxlike walls or has two benzene molecules associated with it in some fashion $(C_{49}H_{43}N_7O_{16})_2\cdot(C_6H_6)_2$: C, 62.09; H, 4.64; N, 9.21. In the absence of X-ray crystallographic data, it is currently unknown which of these two limiting scenarios pertains in the solid state. In solution the trapped guests (i.e., 1,2-dichloroethane or benzene) are in fast exchange with solvent molecules as evidenced by the fact that unchanged chemical shifts were observed by ^{1}H NMR spectroscopy (see Supporting Information). Thus, ensemble **I** cannot be considered as being a permanent chemical "box" or self-assembled receptor for small molecules in solution.[20]

Results from ^{1}H NMR. Further evidence that compounds **1**, **2**, **3**, and **4** self-associate through base pairing came from ^{1}H NMR spectroscopic studies. In a first study, chemical shifts of the imino N−H protons of the uridine moieties of compound **1**, **2**, and **3**, and of guanosine moiety of compound **4**, were compared with those of their control molecules **7a**/**8a**, **12**/**13**, and **19**/**23**, respectively. Two different solvents were used for these comparisons: $CDCl_3$, an aprotic noncompetitive solvent which was expected to favor base pairing, and DMSO-d_6, an aprotic but highly competitive solvent which was expected to disrupt putative hydrogen-bonding interactions. The results of this study are summarized in Table 2.

The significant downfield shifts in $CDCl_3$, $\Delta\delta$ = 5.4 ppm for **1**, 4.1 ppm for **2**, 3.6 ppm for **3**, and 2.9 ppm for **4**, as compared to their respective controls, are most readily interpreted in terms of the presence of strong self-associating interactions mediated through hydrogen-bonds. Supporting this conclusion was the fact that such downfield shifts were not seen in DMSO-d_6 as evidenced by the fact that the chemical shifts of all the complementary compounds are virtually the same as those of their controls. Under these conditions the monomeric species predominate. These are presumably stabilized by solvating interactions involving the DMSO-d_6.

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Table 2. N−H Resonance (ppm) in $CDCl_3$ and DMSO-d_6

	compound									
	7a	**8a**	**1/I**	**2/II**	**12**	**13**	**3/III**	**19**	**23**	**4/IV**
$CDCl_3$	9.22	9.30	14.68	13.58	9.60	9.61	13.22	10.11	10.06	13.52
DMSO-d_6	11.74	11.98	11.60	11.84	11.92	11.86	11.91	11.15	11.10	11.12

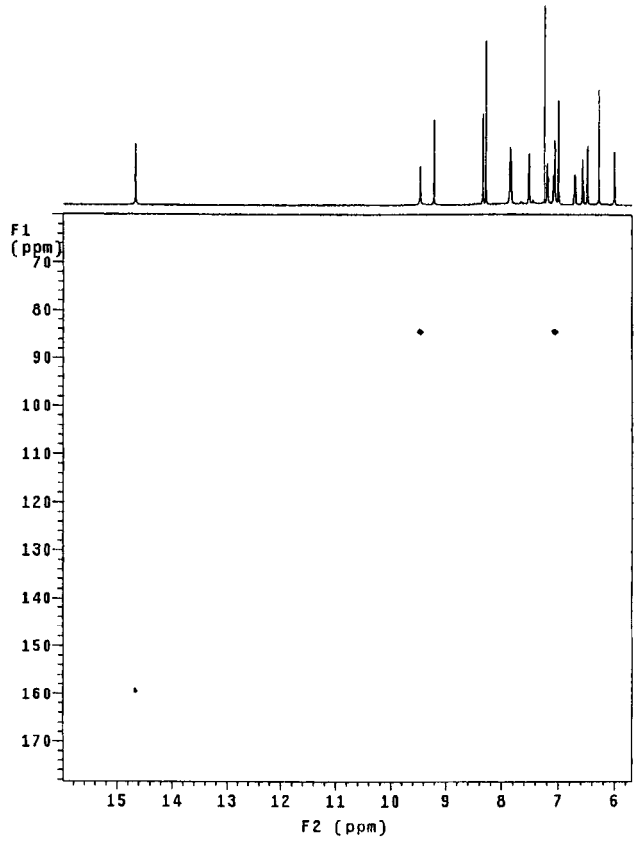

Figure 1. $^{15}N-^{1}H$ HMQC spectrum of **I** at room temperature in $CDCl_3$. A single imino NH proton at 14.7 ppm and two unequivalent amino NH_2 separated by 2.5 ppm are attached to the same nitrogen.

The $^{1}H-^{15}N$ HMQC spectrum of **I** in $CDCl_3$ (Figure 1) provides evidence for the protons resonating at 9.5 and 7.0 ppm being located on the same nitrogen; they are thus assigned to the amino group, NH_2. Both the inequivalence and large separation (~2.5 ppm) of these two amino protons are consistent with rotation about the amino−C4 bond being slow on the NMR time scale in ensemble **I**. Such a slow bond rotation is the result, presumably, of strong hydrogen bond interactions involving the amino group. Support for this conclusion comes from the finding that when DMSO-d_6 is used as the solvent, the two amino protons become equivalent. This result provides prima facie evidence that the inequivalence of the amino group of **I** in $CDCl_3$ is caused by the presence of strong hydrogen bonds.

The ^{1}H NMR spectrum of **2** in $CDCl_3$ is quite different from that of **1** (Figure 2). For instance, the very sharp peak at 14.7 ppm, ascribed to the imino N−H of the uridine moiety of **1**, is replaced by a much broader and upfield shifted peak at 13.7 ppm in the case of **2**. Further, in **2** the two amino protons are found to be equivalent. Considered jointly, these findings are taken as an indication that ensemble **II** is a loosely bound, hydrogen-bonded complex. As pointed out earlier, the only difference between **1** and **2** is the size of the

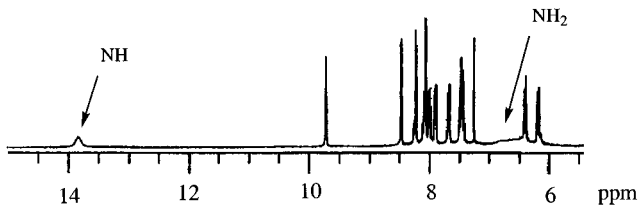

Figure 2. Partial ^{1}H NMR spectrum of **2/II** (300 MHz, $CDCl_3$).

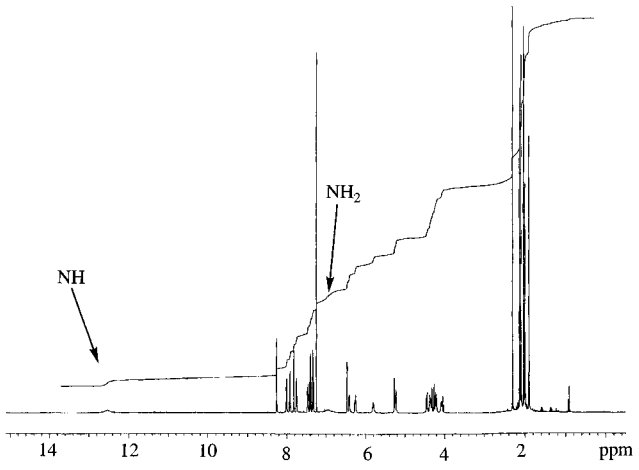

Figure 3. ^{1}H NMR spectrum of **3/III** (500 MHz, $CDCl_3$).

protecting groups on the ribose subunits. Apparently, the larger protecting groups present in monomer **2** lead to the formation of a less-stabilized duplex (**II**).

The duplex formed from **3**, i.e., complex **III**, was also found to be less stable than that formed from **1**. Specifically, the upfield shift of the imino proton, observed in the ^{1}H NMR spectrum of **III** in $CDCl_3$ (Figure 3) as compared with that of **I**, and the equivalence of the two amino protons of **III** are interpreted in terms of the dibenzofuran-based analogue **III** being less stable than the anthracene-based analogue **I**. This conclusion was further supported by 2D-NOESY experiments (Figure 4): For **I**, strong cross-couplings are observed between the imino N−H signal of the uridine moiety and the two inequivalent amino NH_2 signals, as well as between the imino proton N−H and H2 of adenosine. By contrast, such cross-couplings are not seen in the case of **II** and **III** under identical conditions. These results are thus interpreted in terms of the duplex **I** being strongly associated and complexes **II** and **III** being loosely bound.

As pointed out earlier, the only difference between **1** and **3** is the degree of preorganization of the two recognition units. The two nearly parallel recognition units in the anthracene-based system **I** (according to CPK model) seem to be oriented in the ideal geometry for duplex formation. In the dibenzofuran-based system **3**, these same recognition units are constrained to a "V" configuration, where the hydrogen bonds might have to distort to some degree in order to form the duplex **III**. Since hydrogen bonds are directional interactions, the reduced preorganization in the case of **3/III** is believed to be at the root of the lowered duplex stability.

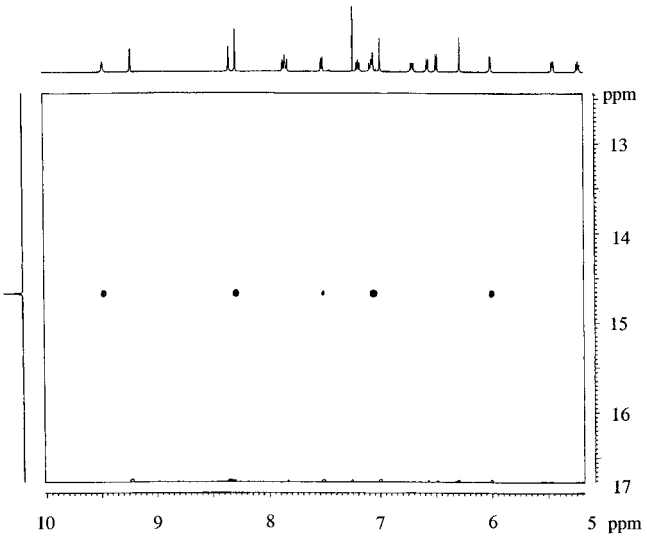

Figure 4. 2D-NOESY spectrum of **I** (500 MHz, $CDCl_3$) showing the strong cross-coupling of the imino NH with the exocyclic amino NH_2 and the H2 proton of adenosine moiety.

Chart 3

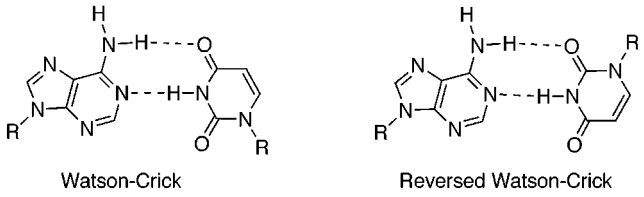

Table 3. ^{13}C Resonances of C4 Carbonyl and C2 Carbonyl of the Uridine Moieties Contained in Ensembles I and III

	compound					
	1/I	**7a**	**8a**	**3/III**	**12**	**13**
C4	162.41	160.48	160.85	162.79	160.85	160.76
C2	149.40	149.35	149.40	149.00	149.20	149.27

^{13}C NMR Studies. Although ^{13}C NMR spectroscopy is not frequently used to study hydrogen-bonded complexes[21] because of the smaller changes in ^{13}C chemical shift observed on binding, it sometimes provides unique information that can complement that obtained from ^{1}H NMR spectroscopic analyses. In the present instance, it was considered that ^{13}C NMR spectroscopy might provide a means of differentiating between Watson−Crick and reversed Watson−Crick binding modes (Chart 3). In the case of the Watson−Crick base pairing model, the imino NH and the C4 carbonyl group of the uridine participate in hydrogen bonding with adenosine. On the other hand, in the reversed Watson−Crick model, it is the C2 carbonyl group plus the imino NH of uridine that interact with adenosine. Therefore, it might be expected that the chemical shifts of C4 and C2 of the uridine moieties in **I** and **III** might differ from those observed in the respective control compounds, namely, **7a**/**8a** and **12**/**13**. Actual experimental findings are summarized in Table 3. These results serve to show that in both **I** and **III** it is the signal of C4 that experiences a significant downfield shift (∼2 ppm) relative to control. By contrast, the chemical shifts of C2 in **I** and **III** remain largely unchanged. These findings are consistent with the C4 carbonyl group, but not the C2 carbonyl group, participating in the hydrogen bond process. In other words, it is a normal Watson−Crick base-pairing interaction and not a reversed one that dominates the recognition processes.

^{1}H NMR Titration. Attempts to estimate quantitatively the thermodynamic parameters, including binding constants for formation of **I**, **II**, **III**, and **IV**, failed due to the simple fact that we were unable to find solution phase conditions for any of the four ensembles in question under which they were dissociated to such a degree that accurate measurements of the binding constants could be carried out. For instance, the chemical shifts of the imino N−H protons for these systems are virtually concentration independent (the chemical shifts of **2** and **3** show small concentration dependences in $CDCl_3$, i.e., ∼0.8 ppm from 10^{-2} to 10^{-4} M) in nonpolar solvents such as $CDCl_3$.[22] Therefore, the dilution method in nonpolar solvent could not be used accurately in this instance.[23] Although the four duplex systems under consideration do show concentration dependence when mixtures of DMSO-d_6/$CDCl_3$ are used as solvents, they do not display concentration dependence in the same solvent mixtures. For instance, **3**/**III** displayed concentration dependence in 5% DMSO-d_6/$CDCl_3$, under which conditions a self-aggregation binding constant of 10.6 M^{-1} was obtained (see Supporting Information for details). By contrast, in this same solvent mixture, no concentration dependence was observed for the NH signals of **1**/**I**. In fact, to calculate a binding constant for **I** accurately, a solvent mixture containing at least 35% DMSO-d_6 in chloroform-*d* had to be used. Under these conditions, however, complexes **II**, **III**, and **IV** were found to be totally dissociated into their respective monomers. Despite these limitations, titration experiments involving the addition of DMSO-d_6 to a solution of **I**, **II**, **III**, and **IV** in $CDCl_3$ were carried out; these studies, it was thought, would still provide valuable information about their self-association, at least in a qualitative sense. Specifically, it was expected that the stronger the complexes, the more DMSO-d_6 would be needed to disrupt the hydrogen-bond interactions. Further details of these experiments are given below.

The relevant region of the ^{1}H NMR spectra of ensemble **I** obtained from the DMSO-d_6 titration experiments are reproduced in Figure 5. In accord with the results discussed earlier, the signal at 14.6 ppm is ascribed to the hydrogen-bonded ensemble **I** while the signal at 11.6 ppm is assigned to the monomeric species **1**. To the extent that such assignments are correct, these spectra clearly indicate that ensemble **I** remains intact with up to 30% (v/v) DMSO-d_6 as cosolvent. However, this same ensemble becomes completely dissociated when the relative DMSO-d_6 concentration reaches 60% or higher. In the regime where the DMSO-d_6 concentration in $CDCl_3$ falls between 35% and 50% v/v, two signals for the imino N−H resonances, corresponding to monomer and duplex-like dimer, were observed.

The fact that two separate signals are seen in the ^{1}H NMR spectrum of ensemble **I** is consistent with exchange between the solvated monomer **1** and dimer **I** being slow

(21) Iwahashi, H.; Kyogoku, Y. *J. Am. Chem. Soc.* **1977**, *99*, 7761.

(22) Compounds **2** and **3** show a small concentration dependence; the chemical shifts changed by 0.8 and 0.3 ppm, respectively, upon moving from 10^{-2} to 10^{-4} M at rt in $CDCl_3$.

(23) (a) Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987. (b) Feeney, J.; Batchelor, J. G.; Albrand, J. P.; Roberts, G. C. K. *J. Magn. Reson.* **1979**, *33*, 519.

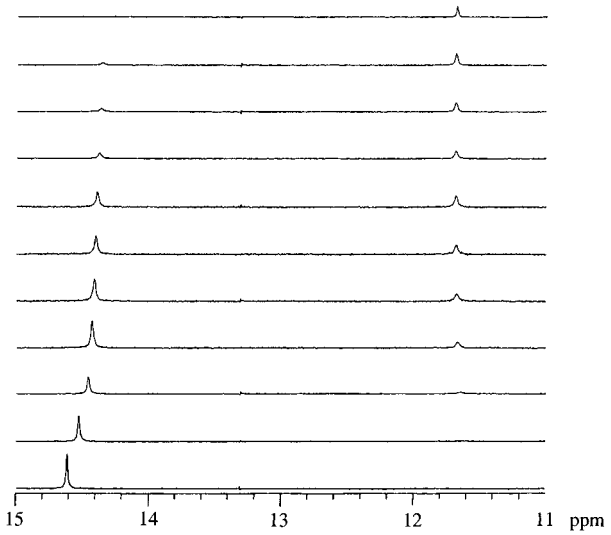

Figure 5. Stacked plots derived from ^{1}H NMR spectroscopic titration studies of **1/I**. The DMSO-d_6 composition in $CDCl_3$ from bottom to top: 10%; 20%; 30%; 35%; 38%; 40%; 42%; 45%; 48%; 50%; 60%.

on the NMR time scale. Such slow exchange is usually observed in cases of very tightly bound complexes.[23] In 45% (v/v) DMSO-d_6/$CDCl_3$, the two uridine NH peaks corresponding to monomer **1** and dimer **I** are sufficiently similar in size that their areas may be determined accurately by integration. This gives the relative ratio of species **1** and **I**, after accounting for stoichiometry. With a knowledge of the total amount of starting ligand **1** (3.94×10^{-2} molar), a self-association constant of 35 ± 5 M^{-1}, corresponding to the formation of **I**, could thus be calculated directly. It was found from this calculation (see Experimental Section for details) that 4 equiv of DMSO are involved in the equilibrium; in other words, each monomeric **1** molecule is solvated by four DMSO molecules. Therefore, the calculated self-association constant of $\sim$35 M^{-1} is an effective one relevant only under these particular mixed solvent conditions. Nonetheless, these studies lead us to conclude that self-association of **I** is favorable not only in pure $CDCl_3$ but also under these mixed solvent conditions.

As demonstrated above, ensemble **I** shows remarkable resistance toward dissociation in the presence of DMSO. By contrast, solutions of ensembles **II**, **III**, and **IV** in $CDCl_3$ can easily be dissociated by the addition of DMSO-d_6. For instance, Figure 6 shows that the very broad signal from the imino NH observed at 13.0 ppm in the ^{1}H NMR spectrum of **II** became sharp when DMSO-d_6 was added. Further, the signal quickly became insensitive to DMSO-d_6 concentration (δ = 11.98 ppm) when 30% DMSO v/v was added to what was initially a pure $CDCl_3$ solution. Such findings are consistent with ensemble **II** being able to survive only a relatively low (<30%) concentration of DMSO before becoming totally dissociated to its mononeric constituent **2**. Such a conclusion, in turn, supports the notion that protecting group steric size plays a critical role in regulating the monomer−dimer equilibrium.

On the basis of a similar analysis, it was determined that ensemble **III** is even less stable; it can only survive 25% DMSO before becoming fully dissociated to its monomer **3**. This conclusion is inferred from the fact that the signal of the imino N−H proton at δ = 13.2 ppm in pure $CDCl_3$ was shifted to 11.9 ppm in 25% DMSO-d_6/$CDCl_3$ (Figure 7) and that the same chemical shift value was obtained when pure DMSO was used as the solvent. These experimental results can be rationalized in terms of the preorganization arguments discussed earlier.

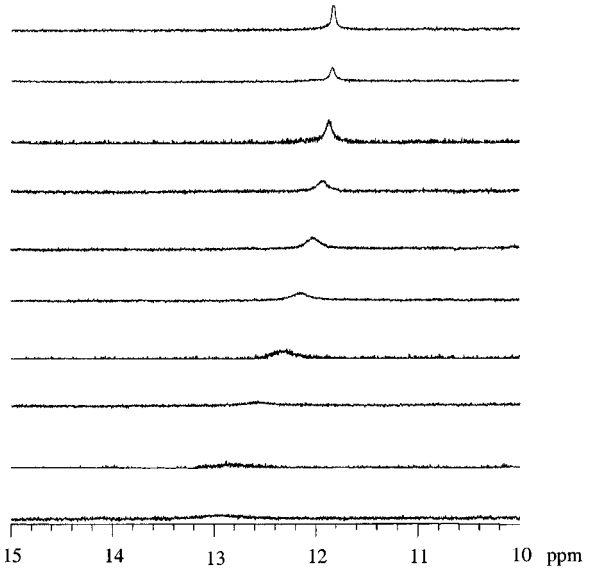

Figure 6. Stacked plots derived from ^{1}H NMR spectroscopic titration studies of **2/II**. The DMSO-d_6 composition in $CDCl_3$ from bottom to top: 0%; 5%; 10%; 15%; 20%; 25%; 30%; 35%; 40%; 50%.

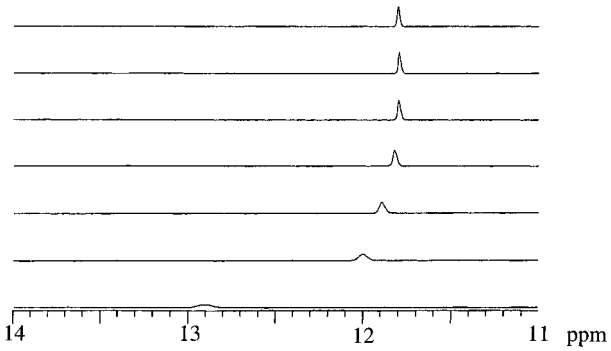

Figure 7. Stacked plots derived from ^{1}H NMR spectroscopic titration studies of **3/III**. The DMSO-d_6 composition in $CDCl_3$ from bottom to top: 0%; 10%; 15%; 20%; 25%; 30%; 35%.

Figure 8 shows the DMSO-based ^{1}H NMR titration profile for the GC analogue **IV**. Unlike ensemble **II**, where the NH signal becomes sharper upon DMSO-d_6 addition, the signal of the imino proton of **IV**, at 13.5 ppm in pure $CDCl_3$, broadens when DMSO-d_6 is added. In fact, this signal disappears (at a δ value of ca. 12.4 ppm) once a DMSO-d_6 concentration $\geq$40% is attained.

It is not surprising that both ensembles **II** and **III** are more easily dissociated upon DMSO addition than ensemble **I**. However, it is somewhat unexpected that it takes less DMSO to dissociate ensemble **IV** than it does to break up duplex **I**, since the former contains 50% more hydrogen bonds than the latter. However, as pointed out earlier, **I** differs from **IV** not only in the number of hydrogen bonds but also in the size of protecting groups. These latter can play a significant role as demonstrated earlier in the case of **I** vs **II**. Apparently, the destabilizing steric effects from the larger protecting groups present in **IV** are sufficient to offset the enthalpy gained

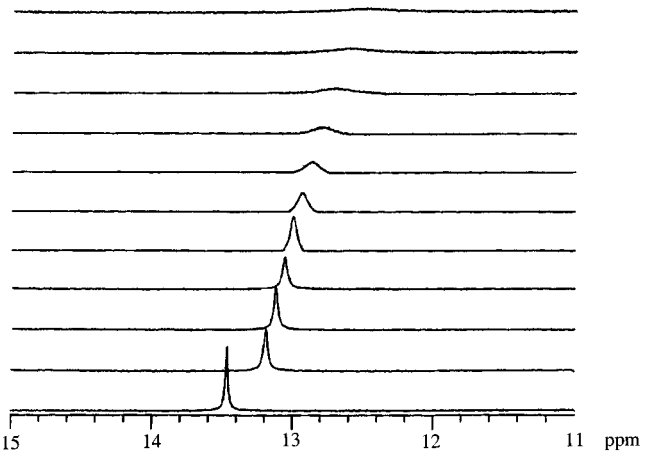

Figure 8. Stacked plots derived from ^{1}H NMR spectroscopic titration studies of **4/IV**. The DMSO-d_6 composition in $CDCl_3$ from bottom to top: 0%; 5%; 10%; 15%; 20%; 25%; 30%; 35%; 40%; 45%; 50%.

from the 50% increase in the number of hydrogen-bonding interactions. When the aggregation properties of **2** and **4**, systems that differ only in the number of available H-bonding sites, are compared, it becomes apparent that more DMSO (~40% vs ~30%) is needed to dissociate the dimer corresponding to **4** (ensemble **IV**) than that derived from **2** (ensemble **II**). This provides a cogent "reminder" that the number of hydrogen bonds still plays a critical role in mediating the aggregation properties of these kinds of self-assembling systems.

Although the exact nature of the above steric hindrance effect is not known, we speculate that it reflects a conformational change involving the two nucleosides. In order for compounds **1**−**4** to form duplexlike structures cooperatively, the two recognition units have to adopt "syn" conformations. The adoption of such conformations may be possible for a system with small protecting groups such as **1**. For compounds **2** and **4**, however, the two bulky ribose groups are forced to adopt a more favorable "anti" conformation to avoid the steric repulsions between the two ribose subunits. As a result, an extra energy barrier has to be overcome before the duplexlike dimer can form.

Temperature-Dependence Studies. In an effort to study more fully the equilibria leading to the formation of ensembles **I**, **II**, **III**, and **IV**, variable temperature ^{1}H NMR studies were undertaken. For ensemble **I**, temperature has little effect on the monomer (**1**) to dimer (**I**) equilibrium in the nonpolar solvent $CDCl_3$,[24] as judged from the invariant ^{1}H NMR spectra recorded between 328 and 218 K (Figure 9).

By contrast, changes in temperature have a drastic effect on the monomer/dimer equilibria of **II**, **III**, and **IV** in nonpolar solvents such as $CDCl_3$ and CD_2Cl_2. For instance, in contrast to system **1** in $CDCl_3$, where only the duplexlike ensemble **I** is observed, system **2** shows strong temperature dependence under the same conditions (Figure 10). A very broad resonance at 280 K splits

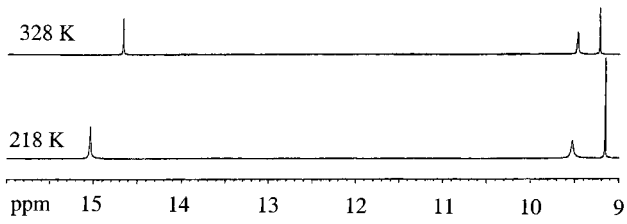

Figure 9. Partial ^{1}H NMR spectra obtained in the course of carrying out a temperature-dependence study of compound **I-(1)** (500 MHz, $CDCl_3$).

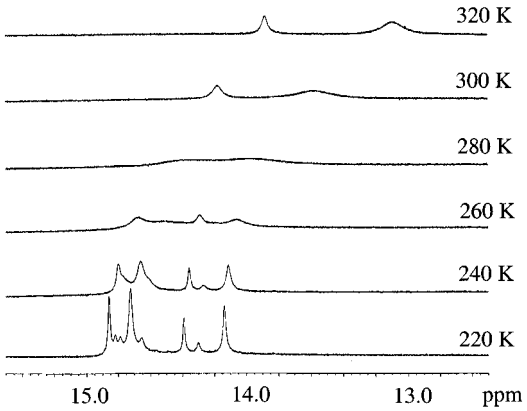

Figure 10. Partial ^{1}H NMR spectra obtained in the course of carrying out a temperature-dependence study of compound **II(2)** (500 MHz, $CDCl_3$).

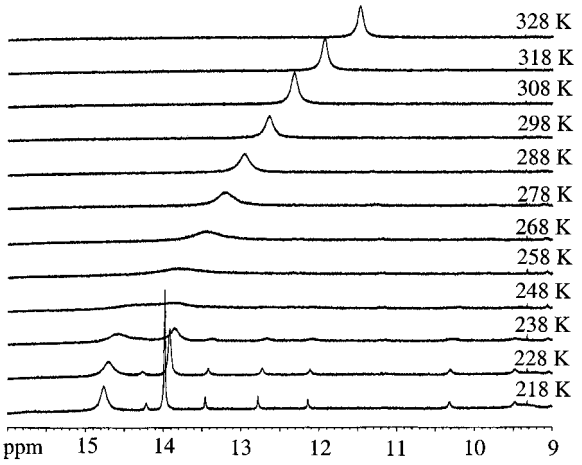

Figure 11. Partial ^{1}H NMR spectra obtained in the course of carrying out a temperature-dependence study of compound **III(3)** (500 MHz, $CDCl_3$).

into two separate peaks at 320 K; the same resonance becomes even more complicated when the temperature decreases. At 220 K, at least six imino NH resonance signals are observed. Such complicated spectra, apparently the results of the presence of a large protecting group on the ribose subunit as discussed earlier, is best interpreted in terms of a scenario wherein the duplexlike ensemble **II** is not the only hydrogen-bonded complex in solution. In other words, some other complex geometries (i.e., trimer, oligomer, etc.) may also exist. These aggregated forms become stable enough at low temperatures that multiple resonances from each corresponding imino NH are observed in the ^{1}H NMR spectrum.

Figure 11 shows the spectra obtained from the temperature-dependence study of system **III**. In analogy to

(24) System **1**/**I** shows a clear temperature dependence in 45% DMSO-d_6/$CDCl_3$: low temperature favors the dimeric species **I**, while high temperature favors the monomeric species **1**. A van't Hoff analysis of the data reveals that ensemble **I** is 14.8 kcal mol^{-1} enthalpically more favorable than the corresponding monomeric species **1**; however, ensemble **I** is also less favored entropically under these particular conditions by 42.3 cal K^{-1} (see Supporting Information for details).

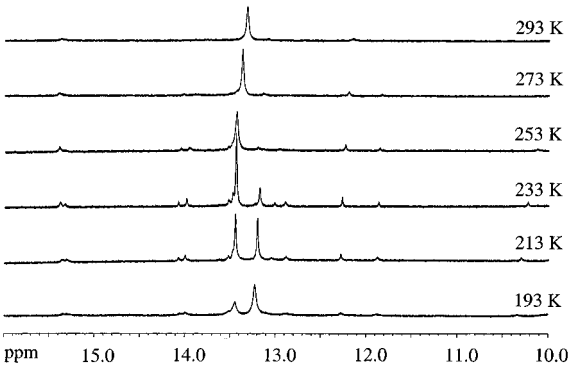

Figure 12. Partial ^{1}H NMR spectra obtained in the course of carrying out a temperature-dependence study of compound **IV(4)** (500 MHz, CD_2Cl_2).

system **II**, only a single broad resonance ascribable to the imino proton of **III** was observed in the ^{1}H NMR spectrum recorded in $CDCl_3$ at 328 K. As the temperature was lowered, increasingly complicated spectra were observed; there are at least six resonances assignable to the imino proton that are observed at 218 K. Such complicated spectra are likely the result of a less ideal preorganization than that which influences the formation of duplexlike structure **I**, as discussed earlier. To the extent this is true, it is considered likely that some other types of complexes, possibly oligomers, are present and that these are competing with the formation of the duplexlike complex **III**. This is especially true at low temperatures, where the exchange of the imino proton among these different states slows down enough on the ^{1}H NMR time scale to give rise to the observed multiple resonances.

In analogy to system **2**, variable temperature ^{1}H NMR spectroscopy of system **4** in CD_2Cl_2 (Figure 12) revealed a single resonance at room temperature and multiple resonances ascribable to the imino N−H's at low temperatures. This temperature-dependent behavior is easily rationalized in terms of the possible existence of conformational isomers (syn and anti) as discussed above. The syn conformation favors the formation of the duplexlike structure **IV** while the anti conformation, it is predicted, leads to formation of linear oligomers.

Conclusion

In summary, we have succeeded in achieving the self-assembly of DNA-like artificial dinucleotide duplex structures by increasing the rigidity and solubility of their components. The structural variations of preorganization, protecting groups, and hydrogen bonds among these systems allowed us to assess better how subtle changes in component structures can dramatically affect the structures and stability of the resulting complexes: Compound **1** self-assembles to form ensemble **I**, a very stable and discrete complex. On the other hand, the complexes derived from the other three monomers (**2**−**4**) (ensembles **II**−**IV**) are not only less stable but also less discrete.

Despite these very concrete conclusions, several intriguing issues regarding ensemble **I** remain unanswered at present: (1) How does **I** bind 2 equiv of 1,2-dichloroethane and benzene? Is this via inclusion or in the form of a clathrate type complex? (2) Why does ensemble **I** selectively bind 2 equiv of benzene instead of dichloromethane when recrystallized from a mixture of both solvents? Presently, we are working to prepare yet-larger systems in an effort to address these issues.

Experimental Section

General Information. The nucleic acid base precursors were purchased from Sigma Chemical Co. All other solvents and reagents were of reagent grade quality and used as received except as noted below. Toluene and tetrahydrofuran (THF) when used as solvents for Pd-catalyzed cross-coupling reactions were distilled from sodium and sodium/benzophenone, respectively. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich Chemical Co. (Sure-Seal). Thin-layer chromatography (TLC) was performed on commercially prepared silica gel 60 F_{254} plates. Column chromatography was performed using Merck silica gel 60 as the solid support unless indicated otherwise.

General Procedure 1: Pd-Catalyzed Cross-Coupling Reactions between a Terminal Alkyne and an Aryl Halide. To a solution of an appropriate alkyne and halide (bromide or iodide) in an argon-degassed mixture of triethylamine (Et_3N) and acetonitrile (MeCN) or THF was added bis(triphenylphosphine)palladium(II) chloride ($PdCl_2(PPh_3)_2$) or tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (3−6 mol % of the limiting reagent) and copper(I) iodide (6−10% mol % equiv). The resulting mixture was then stirred at room temperature (rt) or at an elevated temperature for 2−24 h. After completion of the reaction (monitored by TLC), the solvents were removed under reduced pressure using a rotary evaporator to give a crude product which was purified chromatographically using silica gel as the solid support. Appropriate mixtures of ethyl acetate/hexanes were used as eluent so as to obtain the desired product.

General Procedure 2: Removal of the TMS group(s). To a stirred solution of a trimethylsilyl (TMS)-protected alkyne in methanol or THF was added (1) TBAF (1.2 equiv) at 0 °C and then the solution was warmed to room temperature (2) or KOH (1.5 equiv, 1 M aqueous) at room temperature. After complete consumption of the starting material (determined by TLC), the solution was concentrated by rotary evaporation to give a crude product which was purified by column chromatography on silica gel eluting with the appropriate solvent(s).

General Procedure 3: Pd-Catalyzed Cross-Coupling Reactions between the Tributyltin Derivative of a Terminal Alkyne and the Guanosine Bromide 19. To a round-bottomed flask containing an argon-degassed solution of an alkyne, 8-bromoguanosine **19**, and tributyltin methoxide (excess) in toluene (50 mL) was added $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ (5−8 mol % of the limiting reagent). The resulting mixture was heated at reflux for 10−18 h or until the reaction was deemed complete using TLC analysis. The solvent was then removed under reduced pressure using a rotary evaporator to give a crude product which was purified by column chromatography on silica gel, eluting with ethyl acetate/hexanes and/or ethyl acetate/methanol, as appropriate.

4-Hydroxy-5-[(8-ethynyl-1-anthracenyl)ethynyl]-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one (7a) and 1,8-Bis[4-hydroxyl-5-ethynyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one]anthracene (8a). This compound was prepared by following General Procedure 1, using 1,8-diethynyl anthracene **5** (3.2 g, 14.1 mmol), 5-iodo-2′,3′,5′-tri-*O*-acetyluridine **6a** (3.0 g, 6 mmol), 0.25 g (0.36 mmol) of $PdCl_2(PPh_3)_2$, 0.11 g (0.6 mmol) of CuI, 50 mL of Et_3N, and 50 mL of MeCN (rt, 5 h). Silica gel chromatography first gave (3:2 ethyl acetate/hexanes eluent) product **7a** (3.2 g) in 89% yield and then **8a** (0.3 g) (ethyl acetate eluent) in 10% yield as a byproduct.

For **7a.** ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H), 2.10 (s, 3H), 2.12 (s, 3H), 3.86 (s, 1H), 4.40 (m, 3H), 5.34 (t, 1H), 5.46 (t, 1H), 6.14 (d, 1H), 7.38 (m, 2H), 7.71 (d, 2H), 7.94 (d, 2H), 7.99 (s, 1H), 8.38 (s, 1H), 9.37 (bs, 1H), 9.40 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.4, 20.4, 20.8, 62.8, 70.0, 70.1, 80.2, 81.6, 83.7, 85.4, 87.5, 92.3, 101.8, 120.5, 123.8, 125.0, 127.5, 129.3, 129.4,

130.8, 131.2, 131.3, 131.6, 141.2, 149.4, 160.5, 169.6, 170.0 ppm. LRMSFAB: 594 (M^+), HRCIMS calcd for $C_{33}H_{27}N_2O_9$ 595.1717, found 595.1729 $(M + 1)^+$.

For **8a.** ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 6H), 2.10 (s, 6H), 2.12 (s, 6H), 4.39 (m, 6H), 5.39 (t, 2H), 5.49 (t, 2H), 6.06 (d, 2H), 7.39 (dd, 2H), 7.68 (d, 2H), 7.96 (d, 2H), 7.99 (s, 2H), 8.38 (s, 1H), 9.45 (s, 1H), 9.76 (bs, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.4, 20.7, 62.7, 70.1, 73.5, 80.3, 85.7, 88.6, 91.9, 101.3, 120.8, 124.0, 124.9, 127.5, 129.3, 130.8, 131.2, 142.0, 149.5, 160.9, 169.1, 170.1, 170.3 ppm. LRMSFAB: 963 $(M + 1)^+$, HRMSFAB calcd for $C_{48}H_{42}N_4O_{18}$ 962.2489, found 962.2494. Anal. Calcd for $C_{48}H_{42}N_4O_{18}$: C, 59.88; H, 4.4; N, 5.82. Found: C, 59.73; H, 4.48; N, 5.64.

1-[4-Hydroxyl-5-ethynyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one]-8-[6-amino-8-ethynyl-9-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)purin]anthracene (1). This compound was prepared by following General Procedure 1, using **7a** (3.2 g, 5.39 mmol), 8-bromoadenosine **9a** (3.8 g, 8.05 mmol), 0.23 g (0.32 mmol) of $PdCl_2(PPh_3)_2$, 0.10 g (0.54 mmol) of CuI, 50 mL of Et_3N, and 50 mL of MeCN (60 °C, 20 h). Silica gel chromatography using first 3:1 ethyl acetate/hexane (to remove unreacted **9a**) and then ethyl acetate as the eluent gave product **1** (3.76 g) in 71% yield. ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 3H), 1.87 (s, 3H), 1.94 (s, 3H), 2.16 (s, 3H), 2.20 (s, 3H), 2.40 (s, 3H), 3.96 (m, 2H), 4.11 (m, 2H), 4.58 (m, 2H), 4.87 (m, 1H), 5.26 (m, 1H), 5.47 (m, 1H), 6.02 (d, J = 6.8 Hz, 1H), 6.50 (d, J = 5.3 Hz, 1H), 6.60 (d, J = 5.2 Hz, 1H), 6.70 (m, 1H), 7.10 (m, 2H), 7.20 (t, J = 7.7 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.85 (t, J = 8.5 Hz, 2H), 8.30 (s, 1H), 8.35(s, 1H), 9.22 (s, 1H), 9.49 (bs, 1H), 14.68 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.1, 20.2, 20.6, 21.2, 63.5, 63.7, 70.3, 70.3, 73.0, 74.6, 79.0, 80.2, 83.0, 84.5, 84.7, 88.4, 90.5, 94.3, 99.9, 119.2, 120.0, 120.3, 124.3, 124.9, 126.9, 128.3, 128.4, 130.6, 130.8, 131.1, 131.3, 131.5, 132.2, 136.1, 139.8, 139.8, 148.1, 149.4, 153.2, 155.3, 162.4, 168.4, 169.0, 169.8, 169.9, 170.5 ppm. LRMSFAB: 985 (M^+), HRMSFAB calcd for $C_{49}H_{43}N_7O_{16}$ 985.2766 (M^+ of **1**), found 985.2757. LRMSFAB: 1970 (M^+ of **I**), HRMSFAB calcd for $C_{98}H_{86}N_{14}O_{32}$ 1970.5533 (M^+ of **I**), found 1970.5520. Anal. Calcd for $(C_{49}H_{43}N_7O_{16})_2\cdot(C_6H_6)_2$: C, 62.09; H, 4.64; N, 9.21. Found: C, 62.07; H, 4.65; N, 9.17. Anal. Calcd for $(C_{49}H_{43}N_7O_{16})_2\cdot(C_2H_4Cl_2)_2$: C, 56.5; H, 4.37; N, 9.05; Cl, 6.46. Found: C, 56.51; H, 4.43; N, 8.94; Cl, 6.59.

4-Hydroxy-5-[(8-ethynyl-1-anthracenyl)ethynyl]-1-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)-pyrimidin-2-one (7b). This compound was prepared by following General Procedure 1, using 1,8-diethynylanthracene **5** (1.0 g, 4.4 mmol), 5-iodo-2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyluridine **7b** (1.5 g, 2.1 mmol), 0.090 g (0.12 mmol) of $PdCl_2(PPh_3)_2$, 0.04 g (0.21 mmol) of CuI, and 50 mL of Et_3N (rt, 5 h). Silica gel chromatography (1:4 ethyl acetate/hexanes eluent) gave product **7b** (1.2 g) in 70% yield. ^{1}H NMR ($CDCl_3$): δ 0.04−0.12 (multiple-singlet (ms), 18H), 0.87−0.94 (ms, 27H), 3.72 (s, 1H), 3.74 (m, 1H), 3.97 (d, J = 11.1 Hz, 1H), 4.11 (s, 2H), 4.25 (m, 1H), 6.09 (d, J = 6.3 Hz, 1H), 7.41 (m, 2H), 7.73 (t, J = 7.8 Hz, J = 7.2 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 8.19 (s, 1H), 8.40 (s, 1H), 8.43 (s, 1H), 9.55 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ −5.4, −5.2, −4.7, −4.5, −4.4, 18.0, 18.1, 18.4, 25.8, 25.8, 26.1, 63.0, 72.7, 76.0, 81.5, 83.6, 85.9, 86.5, 88.4, 92.2, 101.0, 120.8, 121.1, 124.4, 124.9, 125.0, 127.4, 128.0, 128.2, 129.3, 130.4, 131.1, 131.4, 131.5, 131.8, 142.1, 149.3, 160.6 ppm. LRMSFAB: 810 (M^+), HRMSFAB calcd for $C_{45}H_{62}N_2O_6Si_3$ 810.3915, found 810.3906.

1-[4-Hydroxy-5-ethynyl-1-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)pyrimidin-2-one]-8-[6-amino-8-ethynyl-9-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)purine]anthracene (2). This compound was prepared by following General Procedure 1, using **7b** (0.8 g, 1.0 mmol), **9b** (0.8 g, 1.1 mmol), 0.04 g (0.06 mmol) of $PdCl_2(PPh_3)_2$, 0.02 g (0.1 mmol) of CuI, and 30 mL Et_3N (60 °C, 4 h). Silica gel chromatography (3:1 ethyl acetate/hexanes eluent) gave product **2** (0.91 g) in 65% yield. ^{1}H NMR ($CDCl_3$): δ −0.65 to 1.05 (ms, 90 H), 3.74−4.22 (m, 9H), 5.10 (m, 1H), 6.17 (d, J = 6.0 Hz, 1H), 6.40 (d, J = 7.5 Hz, 1H), 6.70 (bs, 2H), 7.48 (q, J = 8.1 Hz, 2H), 7.67 (d, J = 6.9 Hz, 1H), 7.89 (d, J = 6.9 Hz), 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.05 (m, 2H), 8.07 (d, J = 16.5 Hz, 1H), 8.21 (s, 1H), 8.45 (s, 1H), 9.71 (s, 1H), 13.82 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ −5.8, −5.5, −5.4, −5.0, −4.9, −4.8, −4.7, −4.5, −4.4, 17.5, 17.7, 17.9, 18.1, 18.3, 18.7, 25.4, 25.6, 25.73, 25.9, 26.0, 26.3, 62.9, 63.3, 72.2, 72.7, 73.1, 83.4, 86.0, 86.14, 87.3, 87.6, 89.3, 91.6, 93.9, 101.2, 119.9, 120.0, 122.0, 124.6, 125.0, 127.4, 128.7, 129.2, 131.2, 131.2, 131.3, 131.5, 132.0, 132.9, 136.2, 140.6, 149.5, 150.2, 152.1, 154.8, 164.1 ppm. LRMSFAB: 1418 $(M + 1)^+$, HRMSFAB calcd for $C_{73}H_{116}N_7O_{10}Si_6$ 1418.7399 $[M + 1]^+$ of **2**, found 1418.7449. LRMSFAB: 2836 $((M + 1)^+$ of **II**), HRMSFAB calcd for $C_{146}H_{231}N_{14}O_{20}Si_{12}$ 2836.4721 $((M + 1)^+$ of **II**), found 2836.4712.

4,6-Diethynyldibenzofuran (11). This compound was prepared by following General Procedure 1, using **10** (10.7 g, 25.5 mmol), TMS-acetylene (5.0 g, 51 mmol), 1.5 g (1.3 mmol) of $Pd(PPh_3)_4$, 0.5 g (2.6 mmol) of CuI, and 100 mL of Et_3N (50 °C, 15 h). Silica gel chromatography (hexanes eluent) gave product (4,6-dibenzofuranyldiethynylene)bis(trimethylsilane) as an intermediate in quantitative yield. LRMSCI(+): 361, HRMSCI(+) calcd for $C_{22}H_{24}OSi_2$ 360.1366, found 360.1365.

The TMS group of this intermediate was removed by reaction with KF (5.35 g, 92 mmol) while the solution was heated in ethanol (300 mL) at reflux for 3 h. After the reaction was allowed to cool to room temperature, the solvent was then removed and the residue taken up in H_2O (200 mL) and extracted with $CDCl_3$ (3 × 100 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by silica gel column chromatography using $CHCl_3$ as the eluent. This gave product **11** (3.8 g) in 80% yield. ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ 82.9, 83.1, 107.5, 121.7, 123.2, 124.5, 131.7, 131.9 ppm.

5-Trimethylsilylethynyl-4-hydroxyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one (14). This compound was prepared by following General Procedure 1, using **6a** (10 g, 20 mmol), TMS-acetylene (3.64 g, 37.1 mmol), 0.84 g (1.2 mmol) of $PdCl_2(PPh_3)_2$, 0.38 g (2 mmol) of CuI, 50 mL of Et_3N, and 50 mL of MeCN (50 °C, 15 h). Silica gel chromatography using 4:3 ethyl acetate/hexanes as the eluent gave the TMS-protected product **14** (0.91 g) in 91% yield. ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 9H), 2.00 (s, 3H), 2.02 (s, 3H), 2.11 (s, 3H), 4.28 (m, 3H), 5.24 (m, 2H), 6.01 (d, 1H), 7.70 (s, 1H), 9.83 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ −0.5, 20.1, 20.2, 20.6, 62.7, 69.9, 73.0, 80.0, 87.1, 95.0, 99.6, 101.1, 141.9, 149.2, 160.7, 169.3, 169.4, 169.8 ppm. LRCI(+)MS: 467 ($[M + 1]^+$), HRCI-(+)MS calcd for $C_{20}H_{27}N_2O_9Si$ 467.1486, found 467.1484.

5-Ethynyl-4-hydroxy-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one (15). This compound was prepared by following General Procedure 2, using **14** (0.91 g, mmol), TBAF (20 mL, 1 M in THF, 20 mmol), and THF (200 mL) (rt, 4 h). Silica gel chromatography (ethyl acetate eluent) gave product **15** (6.4 g) in 88% yield. ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H), 2.12 (s, 3H), 2.20 (s, 3H), 3.23 (s, 1H), 4.40 (m, 3H), 5.36 (m, 2H), 6.09 (d, 1H), 7.31 (s, 1H), 7.87 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.2, 20.3, 20.7, 62.8, 69.9, 73.1, 74.5, 80.1, 82.3, 87.5, 100.0, 142.7, 149.2, 161.0, 169.4, 169.5, 170.0 ppm. LRMSCI: 395 (M^+), HRCIMS(+) calcd for $C_{17}H_{19}N_2O_9$ 395.1091, found 395.1085.

5-[(6-Iodo-4-dibenzofuranyl)ethynyl-4-hydroxyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one (16) and 4,6-Bis[4-hydroxyl-5-ethynyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one]anthracene (13). This compound was prepared by following General Procedure 1, using **10** (5 g, 12 mmol), **15** (2.3 g, 6 mmol), 0.1 g (0.36 mmol) of $PdCl_2(PPh_3)_2$, 0.12 g (0.6 mmol) of CuI, 80 mL of Et_3N, and 80 mL of MeCN (rt, 24 h). Silica gel chromatography using first 2:1 ethyl acetate/hexane and then ethyl acetate as the eluent gave 3.5 g of product **16** (87% yield) and 0.5 g of compound **13** (9% yield) as a byproduct.

For **16**. LRMSFAB: 687 $(M + 1)^+$, HRCIMS(+) calcd for $C_{29}H_{23}N_2O_{10}I$ 686.0397, found 686.0391. This compound was used without further purification in the ensuing step.

For **13.** ^{1}H NMR ($CDCl_3$): δ 2.11 (s, 6H), 2.13 (s, 6H), 2.25 (s, 6H), 4.43 (m, 6H), 5.52 (m, 4H), 6.12 (d, 2H), 7.34 (t, 2H),

7.62 (d, 2H), 7.94 (d, 2H), 8.10 (s, 2H), 9.25 (bs, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.3, 20.39, 20.9, 62.7, 70.2, 73.2, 80.4, 85.4, 87.7, 88.3, 100.9, 107.3, 121.3, 123.1, 124.0, 130.7, 149.2, 155.7, 160.9, 169.6, 169.7, 170.5 ppm. LRMSFAB: 953 (M^+), HRMSFAB calcd for $C_{46}H_{40}N_4O_{19}$ 953.2365, found 953.2348. Anal. Calcd for $C_{46}H_{40}N_4O_{19}$: C, 57.99; H, 4.23; N, 5.88. Found: C, 57.61; H, 4.28; N, 5.82.

5-[(6-TMS-ethynyl-4-dibenzofuranyl)ethynyl]-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl]pyrimidin-2-one (17). This compound was prepared by following General Procedure 1, using **16** (3.5 g, 5.1 mmol), TMS-acetylene (1.0 g, 10.6 mmol), 0.22 g (0.31 mmol) of $PdCl_2(PPh_3)_2$, 0.9 g (0.5 mmol) of CuI, 20 mL of Et_3N, and 20 mL of MeCN (rt, 12 h). Silica gel chromatography (3:2 ethyl acetate/hexanes eluent) gave product **17** (3.2 g) in 96% yield. LRMSFAB: 657 $(M + 1)^+$, HRMSFAB calcd for $C_{34}H_{32}N_2O_{10}Si$ 656.1826, found 656.1823. This compound was used without further purification.

5-[(6-Ethynyl-4-dibenzofuranyl)ethynyl]-1-(2′,3′,5′-tri-*O*-acetyl-*β*-DD-ribofuranosyl]pyrimidin-2-one (12). This compound was prepared by following General Procedure 2, using **17** (3.2 g, mmol), TBAF (7.5 mL, 1 M in THF, 7.5 mmol), and THF (50 mL) (rt, 5 h). Silica gel chromatography (3:2 ethyl acetate/hexane eluent) gave product **12** (2.4 g) in 84% yield. ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H), 2.14 (s, 3H), 2.28 (s, 3H), 3.62 (s, 1H), 4.39 (m, 3H), 5.44 (m, 2H), 6.20 (d, 1H), 7.33 (m, 2H), 7.58 (d, 1H), 7.64 (d, 1H), 7.92 (dd, 2H), 8.05 (s, 1H), 9.50 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.3, 20.4, 21.0, 60.3, 62.6, 69.9, 73.2, 77.8, 88.1, 101.3, 107.2, 107.0, 115.1, 121.4, 123.0, 123.1, 124.0, 131.5, 141.5, 141.5, 149.3, 155.5, 156.2, 160.8, 169.5, 169.6, 170.3 ppm. LRMSFAB: 585 (M^+), HR-CIMS(+) calcd for $C_{31}H_{25}N_2O_{10}$ 585.1509, found 585.1500.

4-[(5-Ethynyl-4-hydroxyl-1-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrimidin-2-one]-6-[6-amino-8-ethynyl-9-(2′,3′,5′-tri-*O*-acetyl-*β*-D-ribofuranosyl)purine]dibenzofuran (3). This compound was prepared by following General Procedure 1, using **12** (2.0 g, 3.4 mmol), **9a** (2.5 g, 5.3 mmol), 0.15 g (0.21 mmol) of $PdCl_2(PPh_3)_2$, 0.7 g (0.37 mmol) of CuI, 20 mL of Et_3N, and 20 mL MeCN (60 °C, 18 h). Silica gel chromatography using first 4:1 ethyl acetate/hexanes (to remove the unreacted **9a**) and then ethyl acetate as the eluent gave product **3** (2.24 g) in 67% yield. ^{1}H NMR ($CDCl_3$): δ 1.87−2.35 (ms, 18H), 4.07−4.46 (m, 6H), 5.21−5.28 (m, 2H), 5.80 (m, 1H), 6.25 (m, 1H), 6.41 (m, 1H), 6.47 (m, 1H), 7.06 (bs, 2H), 7.33 (t, 1H), 7.39 (t, 1H,), 7.45 (d, 1H, J = 7.69 Hz), 7.74 (d, 1H), 7.81 (s, 1H) 7.91 (dd, 1H), 8.00 (d, 1H, J = 7.69 Hz), 8.28 (s, 1H,), 13.02 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.3, 20.4, 20.4, 20.6, 20.7, 21.0, 62.7, 63.1, 69.6, 70.4, 73.4, 74.1, 79.6, 79.7, 82.3, 86.4, 86.6, 88.1, 88.6, 91.0, 100.5, 106.2, 108.2, 119.0, 121.1, 122.7, 123.1, 123.8, 124.4, 129.5, 131.2, 134.9, 141.0, 148.6, 149.0, 152.6, 154.5, 156.36, 156.7, 162.8, 169.3, 169.3, 169.5, 169.8, 170.1, 170.6 ppm. LRMSFAB: 976 (M^+), HRMSFAB calcd for $C_{47}H_{42}N_7O_{17}$ 976.2637, found 976.2634. Anal. Calcd for $C_{47}H_{42}N_7O_{17}$: C, 57.85; H, 4.23; N, 10.05. Found: C, 57.48; H, 4.27; N, 9.92.

***N*²-(*N*′,*N*′-Dimethylformamide)-8-bromo-9-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)purin-6-one (19).** To a 250 mL round-bottomed flask containing a solution of 8-bromoguanosine **18** (7.1 g, 20 mmol) in THF (100 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (4 equiv). The resulting mixture was stirred at room temperature overnight. The residue was purified by chromatographicy (silica gel; 4:1 ethyl acetate/hexane eluent) to give product **19** (3.76 g) in 84% yield. ^{1}H NMR: δ −0.35 to −0.01 (18H), 0.71−0.90 (27H), 3.10 (s, 6H), 3.74 (2H, m), 3.94 (1H, m), 4.26 (1H, m), 5.17 (1H, m), 5.96 (1H, d), 8.38 (1H, s), 10.86 (1H, s). ^{13}C NMR: δ −5.61, −5.45, −5.29, −4.71, −4.58, 17.68, 17.84, 18.10, 25.51, 25.69, 35.20, 41.23, 62.90, 71.25, 72.25, 85.45, 88.55, 121.00, 122.64, 151.66, 156.48, 157.23, 157.43. MSCI(+): 759, HRCI(+) found 759.3160, calcd 759.3116 for $C_{31}H_{60}N_6O_5Si_3Br$.

4-Amino-5-[(8-ethylnyl-1-anthracenyl)ethynyl)-1-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)pyrimidin-4-one (21). This compound was prepared by following General Procedure 1, using **5** (2.3 g, 10 mmol), 5-iodocytidine **20** (4.5 g, 6.3 mmol), 0.26 g (0.37 mmol) of $PdCl_2(PPh_3)_2$, 0.12 g (0.6 mmol) of CuI, 50 mL of Et_3N, and 50 mL of MeCN (rt, 2 h). Silica gel chromatography using first 3:1 hexanes/ethyl acetate and then ethyl acetate as the eluent gave product **21** (3.5 g) in 68% yield. LRMSFAB(+): 810, HRMSFAB(+) calcd for $C_{45}H_{64}N_3O_5Si_3$ 810.4150, found 810.4124. This compound was used directely in the ensuing step without further purification.

1-[4-Amino-5-ethynyl-1-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)pyrimidin-4-one]-8-[*N*²-(*N*′,*N*′-dimethylformamide)-8-ethynyl-9-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)purin-6-one]anthracene (23). This compound was prepared by following General Procedure 3, using 8-bromoguanosine **19** (3.6 g, 4.7 mmol), mono-cytidine-substituted derivative **21** (3.5 g, 4.3 mmol), tributyltin methoxide (3.2 mL, 10 mmol), 0.0.25 g (0.22 mmol) of $Pd(PPh_3)_4$, and 80 mL of toluene (110 °C, 10 h). Silica gel chromatography using first 1:1 and 2:1 ethyl acetate/hexanes (to remove the unreacted **19** and **21**) and then 5:1 ethyl acetate/hexanes as the eluent gave product **23** (2.3 g) in 36% yield. MSFAB(+): 1488, HRFAB(+) calcd for $C_{76}H_{122}N_9O_{10}Si_6$ 1488.7930, found 1488.7957. The product **23** so obtained was used directly without further purification in the following step.

1-[4-Amino-5-ethynyl-1-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)pyrimidin-4-one]-8-[2-amino-8-ethynyl-9-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)purin-6-one]anthracene (4). Compound **23** (2.3 g) was treated with ammonia-saturated methanol (50 mL) at room temperature overnight. The product was purified via silica gel column chromatography using 2:1 hexanes/ethyl acetate as the eluent. This gave **4** in the form of a yellow, fluorescent solid (1.8 g; 81% yield). ^{1}H NMR ($CDCl_3$): δ 0.07−0.2 (ms, 36H), 0.78−0.97 (ms, 54H), 3.77 (bs, 1H), 3.82 (d, J = 9.37 Hz, 2H), 3.99−4.11 (m, 6H), 4.17 (t, J = 4.45 Hz, J = 4.57 Hz, 1H), 4.33 (bs, 1H), 5.37 (bs, 1H), 6.10 (d, J = 4.45 Hz, 1H), 6.24 (d, J = 10.00 Hz, 1H), 6.46 (bs, 1H), 7.46 (m, 2H), 7.81 (dd, J = 6.34 Hz, J = 16.46 Hz, 2H), 8.09 (m, 2H), 8.47 (s, 1H), 9.14 (bs, 1H), 9.27 (s, 1H), 13.37 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ −5.3, −5.7, −5.2, −4.9, −4.8, −4.6, −4.6, −4.4, −4.3, −4.1, 17.9, 17.9, 18.1, 18.2, 18.4, 18.6, 25.8, 25.9, 26.0, 26.0, 26.3, 62.7, 63.3, 71.5, 71.8, 73.3, 84.4, 85.0, 86.2, 86.9, 89.0, 89.1, 92.2, 92.5, 93.4, 118.4, 119.6, 121.2, 123.0, 124.9, 125.0, 128.2, 129.2, 129.9, 130.6, 130.9, 131.3, 131.7, 131.7, 132.1, 132.8, 144.1, 152.4, 153.6, 155.0, 160.1, 163.8 ppm. MSFAB(+): 1434, HRFAB(+) calcd for $C_{73}H_{117}N_8O_{10}Si_6$ 1433.7508, found 1433.7527. For the dimer **IV**: MSFAB-(+) 2870, HRFAB(+) calcd for $C_{146}H_{233}N_{16}O_{20}Si_{12}$ 2866.4939, found 2866.4900. Anal. Calcd for $C_{73}H_{117}N_8O_{10}Si_6$: C, 61.13; H, 8.15; N, 7.81. Found: C, 61.24; H, 8.16; N, 7.87.

***N*²-(*N*′,*N*′-Dimethylformamide)-8-[(8-ethynyl-1-anthracenyl)ethynyl]-9-(2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-*β*-D-ribofuranosyl)purin-6-one (25).** This compound was prepared by following General Procedure 3, using 8-bromoguanosine **19** (5 g, 6.6 mmol), compound **5** (1.5 g, 6.6 mmol), tributyltin methoxide (3.2 g, 10 mmol), 0.0.38 g (0.33 mmol) of $Pd(PPh_3)_4$, and 80 mL of toluene (110 °C, 18 h). Silica gel chramatography (1:1 ethyl acetate/hexanes eluent) gave product **25** (3.1 g) in 52% yield. ^{1}H NMR ($CDCl_3$): δ −0.35, −0.32, −0.28, −0.19, −0.08, −0.04 (ms, 18 H), 0.62, 0.64, 0.73 (ms, 27 H), 3.00 (s, 6H), 3.81 (s, 1H), 3.92 (m, 3H), 4.20 (d, 1H), 5.08 (m, 1H), 6.25 (d, 1H), 7.47 (m, 2H), 7.68 (dd, 2H), 7.86 (dd, 2H), 8.25 (s, 1H), 8.36 (s, 1H), 9.39 (s, 1H), 10.75 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ −5.9, −5.7, −5.2, −4.8, −4.6, −4.6, 17.7, 17.7, 17.9, 25.5, 25.6, 35.1, 41.1, 63.1, 72.2, 72.6, 80.8, 84.5, 84.7, 85.3, 87.7, 92.2, 119.5, 120.7, 121.5, 123.8, 124.6, 124.9, 127.4, 128.1, 128.3, 128.9, 131.3, 131.8, 150.6, 156.9, 157.3, 157.9 ppm. MSFAB(+): 905, HRMSCI(+) calcd for $C_{49}H_{69}N_6O_5Si_3$ 905.4637, found 905.4651.

Alternative Synthesis of 23. Following General Procedure 1, compounds **25** (1.8 g, 2 mmol) and **20** (1.8 g, 2.5 mmol) were treated with 70 mg of $PdCl_2(PPh_3)_2$, 40 mg of CuI, 30 mL of Et_3N, and 20 mL of MeCN (rt, overnight). Silica gel chromatography (2/1 hexanes/ethyl acetate eluent) then gave **23** (2.1 g) in 71% yield.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **2**; MSFAB spectrum of 1/1 mixtures of **1** and **3**; ^{1}H spectrum of **1** and its 1,2-dichloroethane adduct; binding constant data for a mixture of **1**/**I** in 45% DMSO-d_6/$CDCl_3$ and a summary of resultant thermodynamic parameter determinations; quantification of DMSO solvation of the monomeric species **1**; binding constant determination of **3**/**III** by ^{1}H NMR spectroscopic means (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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