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G-Arylated Hydrogen-Bonded Cyclic Tetramer Assemblies with Remarkable Thermodynamic and Kinetic Stability

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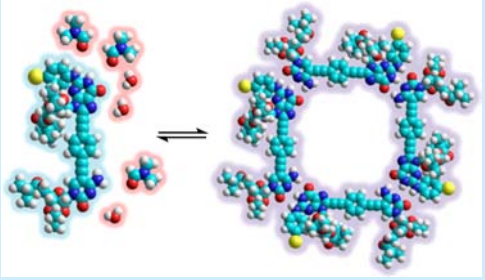
Supporting Information

ABSTRACT: The preparation and self-assembly of novel G−C dinucleoside monomers that are equipped with electron-poor aryl groups at the G-N^2 amino group have been studied. Such monomers associate via Watson−Crick H-bonding into discrete unstrained tetrameric macrocycles that arise as a thermodynamically and kinetically stabilized product in a wide variety of experimental conditions, including very polar solvent environments and low concentrations. G-arylation produces an increased stability of the cyclic assembly, as a result of a subtle interplay between enthalpic and entropic effects involving the solvent coordination sphere.



Macrocycles are aesthetically appealing chemical structures that offer manifold possibilities in diverse fields.[1] Shape-persistent covalent macrocycles, as well as their organized 2D porous networks[2] or 1D stacked nanotubes,[3] have been employed in organic electronics,[4] inclusion chemistry, sensing and catalysis,[5] rotaxane and catenane assembly,[1] or as nanomembranes and synthetic ion channels.[6]

As opposed to covalent methods,[1,4,7] noncovalent synthesis can be viewed as a straightforward and versatile approach toward well-defined macrocycles.[8] The idea is simple: one or several monomers are equipped with supramolecular motifs that contain the information to self-assemble in a single cyclic structure under thermodynamic control. However, the resulting supramolecular macrocycles are not as robust and persistent as their covalent analogues and achieving complete selectivity is a challenging task that demands careful molecular design.[9] Unbound monomers, noncyclic oligomers, or other cyclic structures often compete with the targeted macrocycle, and the relative weight of each species is highly sensitive to the experimental conditions: solvent, concentration, and temperature. Ideally, in order to reach close to quantitative amounts of a given cyclic structure, one should maximize the strength of the intermolecular interactions, as well as minimize the strain generated upon cyclization and the possibilities for alternative monomer conformations.

We recently described[10] the preparation of discrete H-bonded cyclic tetramers[11,12] (Figure 1) from a rigid monomer ($\mathbf{GC_H}$) that is substituted with complementary nucleosides,[13] guanosine (G) and cytidine (C), at both termini.[10] Watson−Crick G−C H-bonding pairing affords an unstrained square-shaped assembly with high fidelity in a broad number of experimental conditions. Here, we extend our studies to related monomers ($\mathbf{GC_{Ar1}}$ and $\mathbf{GC_{Ar2}}$) in which we introduce *p*-substituted electron-poor aryl groups at the G-N^2 via palladium-catalyzed C−N cross-coupling. The objective of this monomer modification is to enhance the stability of the cyclic assemblies by increasing the H-bonding donor ability of the G-amine proton. The resulting tetrameric macrocycles exhibit an impressive thermodynamic and kinetic stability and are able to persist even in highly polar solvent environments.

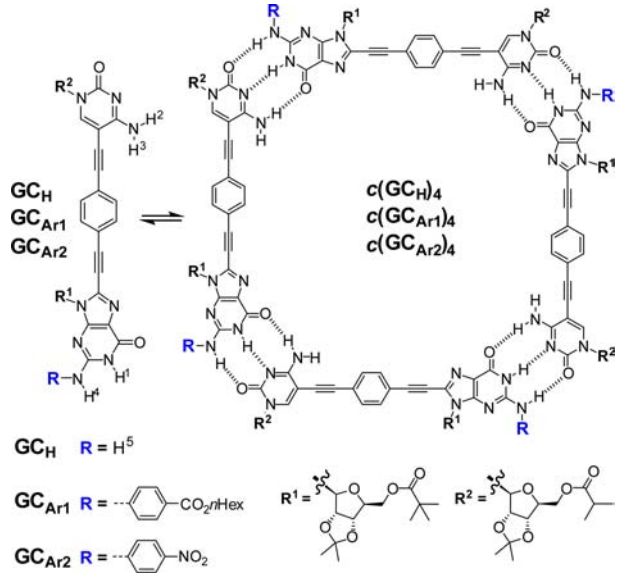


Figure 1. Chemical structure of monomers $\mathbf{GC_H}$, $\mathbf{GC_{Ar1}}$, and $\mathbf{GC_{Ar2}}$ and their corresponding cyclic tetramer assemblies $c(\mathbf{GC_H})_4$, $c(\mathbf{GC_{Ar1}})_4$, and $c(\mathbf{GC_{Ar2}})_4$ studied in this work.

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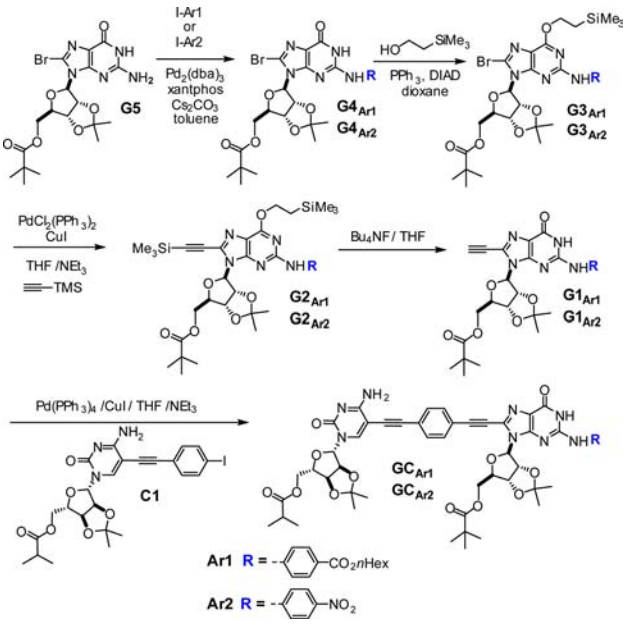
The synthesis of $\mathbf{GC_{Ar1}}$ and $\mathbf{GC_{Ar2}}$ followed a similar route to that reported for $\mathbf{GC_H}$ (Scheme 1).[10,14] The key palladium-

Scheme 1. Synthesis of Monomers $\mathbf{GC_{Ar1}}$ and $\mathbf{GC_{Ar2}}$



catalyzed *N*-arylation reaction[15] with the corresponding iodoarenes was essayed over different G substrates, trying to achieve the most straightforward synthetic path.[16] The best results were obtained when performing the reaction on **G5**,[14] leading to *N*-arylated compounds $\mathbf{G4_{Ar1}}$ and $\mathbf{G4_{Ar2}}$. Due to the low reactivity of bromoguanosines,[17] the oxidative addition is fully selective on the iodoarenes at this step. The G-carbonyl group of these products was then protected as a trimethylsilylethoxy moiety in order to carry out the Sonogashira reaction on $\mathbf{G3_{Ar1}}$ and $\mathbf{G3_{Ar2}}$.[17] Deprotection of the silyl groups of $\mathbf{G2_{Ar1}}$ and $\mathbf{G2_{Ar2}}$ in the presence of tetrabutylammonium fluoride afforded $\mathbf{G1_{Ar1}}$ and $\mathbf{G1_{Ar2}}$, which were then subjected to another palladium-catalyzed coupling with the 5-substituted pyrimidine nucleoside **C1**, whose synthesis has been recently reported by us.[10,14] This reaction led to final monomers $\mathbf{GC_{Ar1}}$ and $\mathbf{GC_{Ar2}}$. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, and HR-MS techniques.[16]

Solutions of $\mathbf{GC_H}$, $\mathbf{GC_{Ar1}}$, or $\mathbf{GC_{Ar2}}$ (10^{-1} to 10^{-3} M) in nonpolar solvents, such as $CDCl_3$, $CDCl_2CDCl_2$, CD_2Cl_2, or THF-D_8, resulted in ^{1}H NMR spectra that revealed a single set of proton resonances which are characteristic of G−C association (Figures 2a and S1). The H-bonded G-H^1 amide and the C-H^2 amine signals are found around 13.5 and 10.0 ppm, respectively. The main difference between the three compounds is the chemical shift of the H-bonded G-H^4 amine proton. Whereas for $\mathbf{GC_H}$ the G-amine protons are found as a broad coalesced signal at 298 K that splits in two sharp signals at 8.5 (H^4) and 5.4 (H^5) ppm below 273 K,[16,18] $\mathbf{GC_{Ar1}}$ and $\mathbf{GC_{Ar2}}$ showed sharp peaks at room temperature close to 11 ppm. The shape and position of these three H-bonded signals are not sensitive to concentration, temperature, or solvent, indicating strong association in apolar solvents. Additionally, NOESY experiments showed cross-peaks between the H-bonded protons, hence confirming G−C association.

The situation is different in polar solvents such as DMSO-D_6 or DMF-D_7 (Figures 2a and S1). The addition of increasing

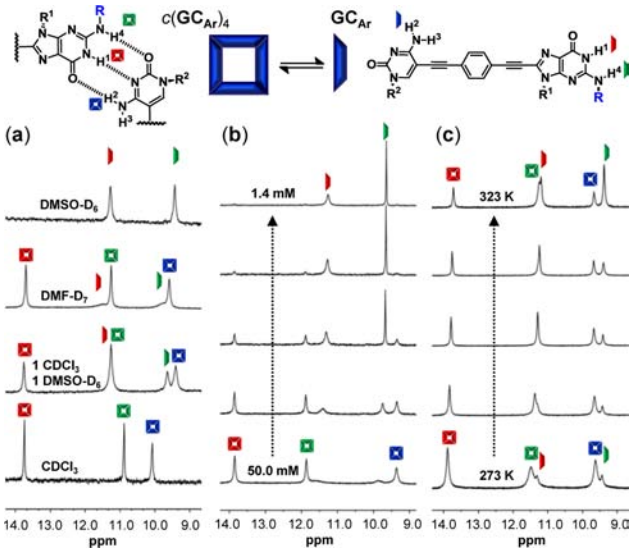


Figure 2. Monomer−cyclic tetramer equilibria in polar solvents. Downfield region of the ^{1}H NMR spectrum showing the H^1, H^2 and H^4 signals as a function of (a) solvent nature ($\mathbf{GC_{Ar1}}$; C = *ca.* 10^{-2} M; T = 298 K), (b) concentration in 1:1 $CDCl_3$/DMSO-D_6 ($\mathbf{GC_{Ar2}}$; T = 298 K), and (c) temperature in 1:1 $CDCl_3$/DMSO-D_6 ($\mathbf{GC_{Ar1}}$; C = 10^{-2} M).

amounts of DMSO to $CDCl_3$ solutions of $\mathbf{GC_{Ar1}}$ or $\mathbf{GC_{Ar2}}$ resulted in the progressive dissociation of the H-bonded species. At the end of these titrations, in 100% DMSO-D_6, $\mathbf{GC_{Ar1}}$ or $\mathbf{GC_{Ar2}}$ displayed H^1, H^2, and H^4 signals at around 11.3, 7.9, and 9.4 ppm, respectively, which are characteristic of monomeric species H-bound to solvent molecules.

Further experiments were carried out in 100% DMF-D_7 and a 50% $CDCl_3$/50% DMSO-D_6 solvent mixture, where we observed a slow equilibrium between two main species: monomer and cyclic tetramer. No other intermediate supramolecular species was detected in these experiments, highlighting the cooperative nature of the cyclic assembly process. Exchange kinetics was studied in more detail by EXSY in DMF-D_7 (Figure S2), confirming remarkably slow monomer−tetramer exchange processes in all cases. Concentration-dependent experiments within the 10^{-1}−10^{-3} M range afforded the cyclotetramerization constants (K_T; Figures 2b and S3), while temperature-dependent experiments in the 323 to 273 K range allowed us to estimate the enthalpic (ΔH) and entropic (ΔS) changes of the assembly process in these polar solvents (Figures 2c and S4). These kinetic and thermodynamic parameters are compared for the 3 compounds in Table 1.

The cyclotetramerization process of $\mathbf{GC_{Ar1}}$ and $\mathbf{GC_{Ar2}}$ was also studied by absorption, emission, and circular dichroism (CD) spectroscopy in THF as a function of sample concentration and temperature (Figures 3, S5, and S6). As was observed for $\mathbf{GC_H}$, when these chiral *N*-arylated monomers associate in macrocycles at high concentrations or low temperatures, a red-shifted absorption shoulder around 395 nm, red-shifted emission maxima, and, significantly, a Cotton CD effect were noticed. The spectroscopic changes monitored in these dilution and cooling experiments were fitted to appropriate models in order to obtain the most relevant thermodynamic parameters in THF (K_T, ΔH, and ΔS; Figures S5 and S6), which are also listed in Table 1.

The exceptional thermodynamic and kinetic stability of our self-assembled macrocycles, evidenced even in highly polar

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Table 1. Thermodynamic and Kinetic Parameters Calculated for the Cyclotetramerization Process of GC_H, GC_{Ar1}, and GC_{Ar2} in Different Solvents[10]

solvent	compd	K_T[a]/M^{-3}	ΔH[b]/ kJ mol^{-1}	ΔS[b]/ J mol^{-1} K^{-1}	τ[c]/ s^{-1}
1:1 $CDCl_3$/ DMSO-D_6	GC_H	2.9×10^5	−142	−387	
	GC_{Ar1}	7.8×10^5	−101	−240	
	GC_{Ar2}	7.4×10^5	−93	−224	
DMF-D_7	GC_H	2.3×10^5	−155	−425	3.0
	GC_{Ar1}	9.6×10^5	−86	−190	7.1
	GC_{Ar2}	6.4×10^5	−101	−247	3.8
THF	GC_H	1.0×10^{15}	−225	−465	
	GC_{Ar1}	4.6×10^{16}	−196	−347	
	GC_{Ar2}	5.9×10^{16}	−221	−407	

[a]From dilution experiments (Figures S3 and S5; Table S1). [b]From a van't Hoff analysis of the cooling experiments (Figures S4 and S6; Table S2). [c]From EXSY experiments (Figure S2). A more detailed table including errors and other parameters can be found in the Supporting Information (Table S3).

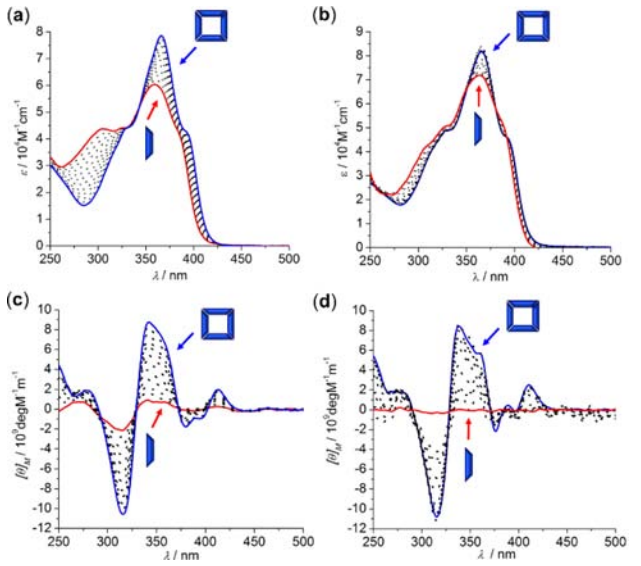

Figure 3. Absorption (a,b) and CD (c,d) changes of GC_{Ar1} in THF as a function of temperature ((a,c) from 328 to 273 K; $C = 1.25 \times 10^{-5}$ M) or the concentration ((b,d) from 2×10^{-4} to 1×10^{-6} M; $T = 298$ K).

environments, can only be compared with the strongest hydrogen-bonded systems.[19] Monomer−tetramer kinetic exchange is remarkably slow in the NMR time scale and comparable for the three molecules. Such a slow process resembles guanosine exchange in G-quadruplexes, where the nucleobase is also hydrogen-bonded in cyclic complexed systems.[20] Tetramerization constants in DMF or 1:1 $CHCl_3$/DMSO are on the order of 10^5−10^6 M^{-3}, which leads to individual G−C association constants of about 20−30 M^{-1}. A G−C association constant of 3.7 M^{-1} was previously determined in polar solvents such as DMSO.[21]

The data presented in Table 1 also reveal that the cyclic tetramers assembled from monomers GC_{Ar1} or GC_{Ar2} are indeed more stable than those of GC_H, affording higher cyclotetramerization constants. In addition, the examination of the NMR and optical spectroscopic trends clearly reveals a higher endurance of GC_{Ar1} or GC_{Ar2} toward dilution or high temperatures.[16] These qualitative observations are translated into the quantitative C_{50} and T_{50} parameters, displayed in Table S3, which stand for the concentration or temperature, respectively, at which half of the molecules are assembled into cyclic tetramers. However, a more careful inspection of the data shown in Table 1 reveals that the origin of such increased stability is not actually coming from a stronger H-bonding of the G unit in the arylated monomers, which would be reflected in a gain in enthalpy upon G−C H-bonding. Instead, such stabilization is mainly caused by the decrease in the absolute value of the entropic term. This effect must be interpreted taking the entire system, including the solvent molecules (DMSO, DMF, THF, and residual H_2O), as a whole.

Globally, it is clear that tetramerization is driven by an increase in enthalpy due to the formation of 6 G−C H-bonds per monomer in the cyclic assembly. ΔH is therefore always negative, and its absolute value increases in less polar solvents (see Table 1). We expected the *N*-arylated products to lead to higher ΔH values than GC_H, since the G-H^4 amine proton becomes more acidic and would participate in stronger H-bonds with the C base in the assembly. However, such a G-H^4 proton in the GC_{Ar1} or GC_{Ar2} monomers must also bind strongly to solvent molecules, especially if they are good H-bonding acceptors like DMSO or DMF. This results in the attenuation of this enthalpic effect in these strongly coordinating solvents.

On the other hand, as it is found in most supramolecular systems, the association of 4 molecules leads to the expected negative ΔS values. But again we should take into account the solvent molecules, H-bound to specific sites of the G-unit in reactants and products. Solvation is logically more important in the monomer state, as there is a higher number of available H-bonding donor and acceptor groups, and this introduces some order in the solvation sphere of the monomer. Binding to the C unit upon cyclotetramerization blocks some of these H-bonding groups, and the solvation sphere becomes more disordered in the associated state. This contributes to a milder decrease in entropy upon association, which is again more patent in polar environments, DMSO or DMF, compared to THF. Let us now compare this effect in GC_H and GC_{Ar1}/GC_{Ar2}. The presence of the aryl group in GC_{Ar1}/GC_{Ar2} leads to different conformations in the monomer state that can be efficiently solvated by the polar molecules. Two of these conformations (*A* and *B*) are depicted in Figure 4. Theoretical calculations (DFT; B3LYP/6-31G) select conformation *A* as being more stable,[16] likely due to steric effects between the amide and aromatic protons in conformation *B*, the gain in conjugation between pyrimidine and phenyl rings, and the formation of an intramolecular H-bond between the *ortho*-aryl proton and the G-N^3 lone pair. Now, when GC_{Ar1}/GC_{Ar2} associate, H-bonding to C necessarily fixes conformation *A* and this produces a sterically crowded region around the Watson−Crick pair that heavily hampers solvation. Hence, we think that the solvation sphere around the GC_{Ar1}/GC_{Ar2} tetramers suffers a higher alteration than that of GC_H upon cycle formation, resulting in smaller ΔS values in polar solvents.

In short, although the differences are not very large, the presence of the electron-poor aryl substituents at the G-N^2 amino group increases the stability of the tetrameric macrocycles, which arise as the main supramolecular product even in polar environments or low concentrations where H-bonding self-assembly is considerably weakened. From the thermodynamic parameters extracted from NMR and optical spectroscopy experiments in solvents of different polarity, we noted a

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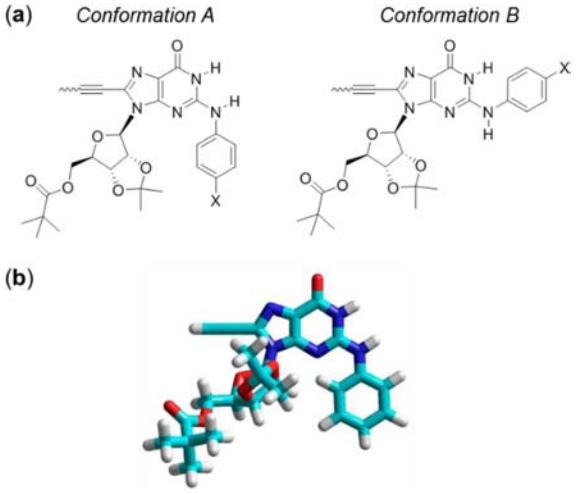

Figure 4. (a) Structure of two possible conformations (*A* and *B*) for the aryl group in GC_{Ar1}/GC_{Ar2}. (b) Energy minimized structure (DFT; B3LYP/6-31G) obtained for an arylated G model.

subtle interplay between enthalpic and entropic effects that involve not only the GC_H or GC_{Ar1}/GC_{Ar2} supramolecular systems but also their solvent coordination sphere.[22]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, ^1H and ^{13}C NMR spectra, and HRMS for novel compounds. NMR, spectroscopic UV−vis, and CD data as a function of temperature and concentration along with the methods employed to analyze the monomer−cyclic tetramer equilibrium (thermodynamic and kinetic parameters). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01042.

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Notes

The authors declare no competing financial interest.

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