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Synthesis and Complementary Self-association of Novel Lipophilic π-Conjugated Nucleoside Oligomers

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A series of lipophilic nucleosides comprising natural and non-natural bases that are π-conjugated to a short oligophenylene-ethynylene fragment has been synthesized. These bases comprise guanosine, *iso*guanosine, 2-aminoadenosine as purine heterocycles, and cytidine, *iso*cytosine and uridine as complementary pyrimidine bases. The hydrogen-bonding dimerization and association processes between complementary bases were as well studied by ^{1}H NMR and absorption spectroscopies in order to obtain the relevant association constants.

Introduction

The field of supramolecular chemistry and molecular self-assembly[1] continues to grow and expand over physical and biological disciplines more than 30 years after its solid establishment in the 80's.[2-4] Among the different non-covalent interactions employed to build self-assembled complexes and nanostructures, hydrogen-bonding plays a central role both in artificial and biological systems.[5-8] Hydrogen-bonds are established when a donor moiety with an available acidic hydrogen atom interacts with an acceptor unit bearing available non-bonding electron lone pairs. This interaction is as a result highly selective and directional, and its strength can be tuned as a function of the chemical nature of the hydrogen-bonding donor and acceptor functions, as well as on their number and sequence in a particular molecular fragment.[9-14]
The design of chemical moieties having specific patterns of hydrogen-bonding donor and acceptor units has been exploited by supramolecular chemists to assemble one or more molecular components and thus construct well-defined systems with large binding constants and high fidelities.[15-19] Much of the inspiration here comes from the double strand assembly in DNA, which employs two base pairs with complementary double (adenine-thymine) or triple (guanine-cytosine) hydrogen-bonding patterns.[20,21] Therefore, the synthesis and binding studies of related heterocyclic units bearing two, three, four, or more hydrogen-bonding donor or acceptor points has been a subject of intense research during the last years.[9-14] These units are indeed treated as "supramolecular directors", able to bring together specific molecular components in a geometrically defined arrangement in order to obtain the target nanosized assemblies, where in many cases hydrogen-bonding interactions cooperate with additional weak non-covalent forces (like π–π stacking, ionic or solvophobic interactions).[7,8,16-18,21]
Here, we report the synthesis of a series of lipophilic nucleosides comprising natural and non-natural nucleobases that are π-conjugated to a short oligophenylene-ethynylene fragment (Figure 1). Guanosine (**G**), *iso*guanosine, (**iG**) and 2,6-diaminopurine or 2-aminoadenosine (DAP) (**A**) were employed as purine bases and cytidine (**C**), *iso*cytosine (**iC**) and uridine (**U**) as complementary pyrimidine heterocycles. The ribose in these nucleosides has been substituted by bulky groups in order to prevent stacking and provide characteristic ^{1}H NMR signals. In this work we also study the hydrogen-bonding dimerization and hetero-association processes between complementary units (**G-C**, **iG-iC**, **G-iC**, **iG-C** and **A-U**) by both ^{1}H NMR and absorption spectroscopies, and analyze the binding isotherms by adequate fitting programs in order to obtain the relevant association constants.[22] Guanine-cytosine and adenine or 2-aminoadenine-uracile binding has already been studied by a number of authors,[23-27] so this work offers new quantitative data on their association constants studied and analyzed by diverse methods. However, to the best of our knowledge, no data has been reported so far on the association between *iso*guanine and *iso*cytosine in organic solvents, or on the interactions between these non-natural bases and cytosine or guanine.

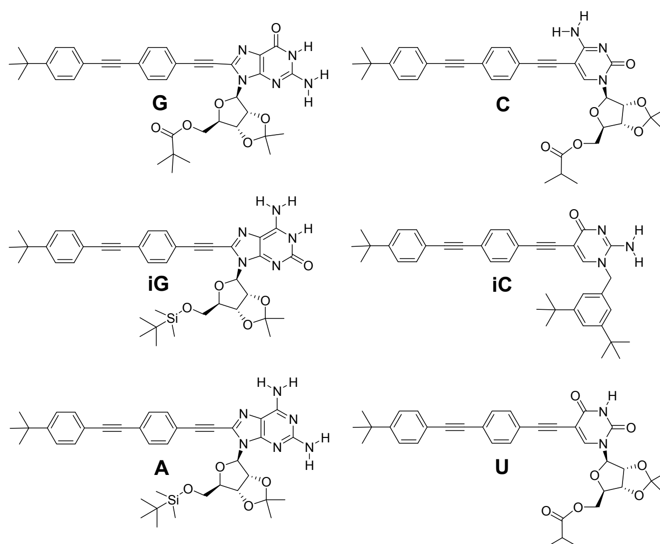
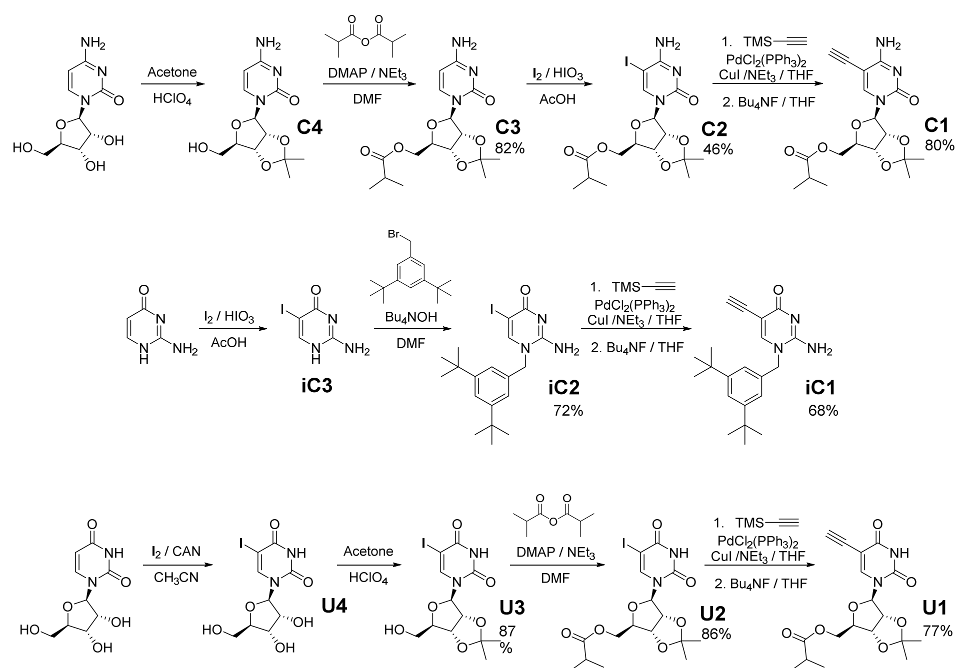


Figure 1. Structure of lipophilic nucleosides **G**, **C**, **iG**, **iC**, **A** (being actually a 2,6-diaminopurine (DAP)) and **U**.



Scheme 1. Synthesis of ethynyl-substituted pyrimidine nucleosides **C1**, **iC1** and **U1**.

Results and discussion

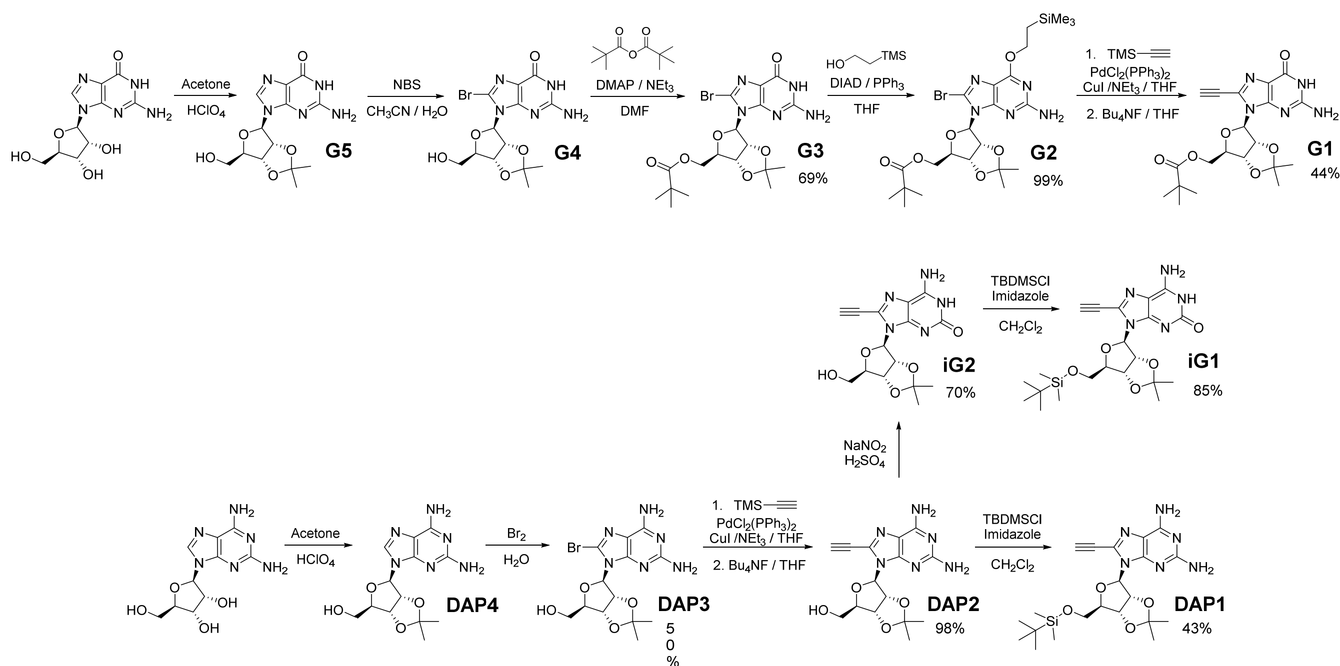
Synthesis of Lipophilic Nucleosides

Lipophilic nucleosides **G**, **C**, **iG**, **iC**, **A** (being actually a 2,6-diaminopurine (DAP)) and **U** were obtained through a two-step coupling procedure between 1,4-diiodobenzene, 4-*tert*butylphenylacetylene, and the corresponding acetylenic base derivatives (**G1**, **C1**, **iG1**, **iC1**, **DAP1** and **U1**). The preparation of these ethynyl-substituted bases (see Schemes 1 and 2) started from the commercial pristine nucleosides and involved a series of synthetic steps, some of them adapted from those found in the literature, that were similar for all the nucleobases.[28]

First of all, the ribose unit was functionalized with bulky, lipophilic groups in order to avoid undesired aggregation and to provide characteristic signals in ^{1}H NMR.[29,30] For instance, the 2' and 3' ribose alcohols were protected as an acetonide group,[31,32] while the 5' position was functionalized as a *tert*butyl ester (**G1**), an *iso*propyl ester (**C1**, **U1**)[33] or a TBDMS group (**iG1**, **DAP1**).[34,35] The only exception is **iC1**, which was prepared from commercial isocytosine and was equipped with a 3,5-di*tert*butylbenzyl group, instead of the natural ribose, *via* a nucleophilic substitution reaction with the corresponding benzyl bromide.[36] This reaction led as well to the N(3)- and O(4)-alkylated products in minor amounts.

A second, common reaction for all nucleosides is halogenation. Pyrimidines were selectively iodinated at C-5[37-39] whereas purines were brominated at C-8.[40] As can be observed from Schemes 1 and 2, this halogenation reaction was performed at different stages and with different methods for each nucleobase. The main reason for this is simply because, among the many variants we tried, we chose the synthetic routes that afforded the highest yields and the easiest purification protocols at some specific steps. For instance, in the route towards **iC1** and **U1**, iodination is the first step because the product is efficiently isolated by straightforward filtration. For **C1**, that was not the case and, in contrast, we preferred to have the ribose completely functionalized in order to achieve a higher overall yield. If we now turn our attention to the purine nucleosides (Scheme 2), bromination is the second step in the route to **G1** and **DAP1** (or **iG1**), just after 2',3'-diol protection. The reason is because the C-8 halogenated purine nucleosides are rather sensitive to depurination in acidic conditions.[41] Hence, when these two steps were inverted, that is, when guanosine or 2-aminoadenine was instead brominated in first instance and then reacted with acetone in the presence of $HClO_4$ or other acids, the C-N glicosidic bond was cleaved quantitatively.

Finally, all the halogenated bases were subjected to a Sonogashira coupling procedure[42,43] with trimethylsilyl-acetylene, followed by fluoride-mediated TMS deprotection. 5-

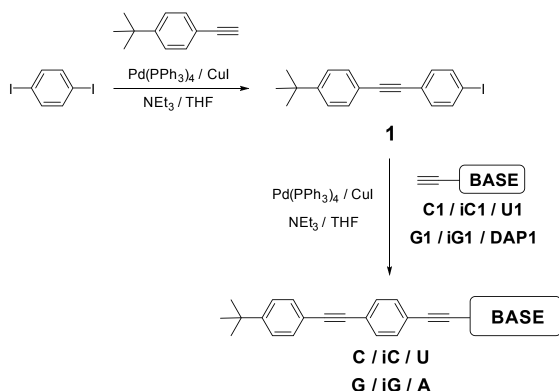


Scheme 2. Synthesis of ethynyl-substituted purine nucleosides **G1**, **iG1** and **DAP1**.

Iodopyrimidines were much more reactive in these Pd-catalyzed couplings than 8-bromopurines. An extreme case was 8-bromoguanosine. All of our attempts to perform a Sonogashira reaction on **G4** or **G3** were unsuccessful and the starting material was recovered instead. There are in fact many examples in the literature that report on the low reactivity of the guanine heterocycle in metal-mediated oxidative addition processes.[44] The low oxidation potential of this base or its ability to coordinate organometallic catalytic species are cited among the causes that would explain such lack of reactivity. The best solution in our hands was the protection of the G-carbonyl group in **G3** as a trimethylsilylethoxy group,[45] in the presence of DIAD and PPh_3, to yield **G2**, which was now active in Pd-catalyzed couplings. Removal of the two TMS protecting groups was achieved in a single step in the presence of Bu_4NF to produce **G1**. Probably, the preparation of 8-iodopurines would have been a better alternative for a more efficient Sonogashira coupling, but their synthesis was found to be problematic for several reasons. First of all, 8-iodopurine nucleosides are more sensitive to depurination (see above).[41] Second, the electrophilic substitution reaction with iodine is a rather low-yielding reaction that may afford undesired products coming from nucleophilic attack to the activated C-8 position. For instance, our attempts to iodinate **G5** resulted in intramolecular attack of the 5'-OH group to the C-8 position to produce the corresponding cyclic ether.[46] On the other hand, all of our efforts to iodinate a guanosine derivative with a fully protected ribose were unsuccessful.

The *iso*guanosine non-natural nucleoside can be obtained from 2,6-diaminopurine in a single step by selective hydrolysis at C-2 *via* a diazonium intermediate.[47] For the sake of simplicity, we wanted to perform this process at the level of **DAP1** but, unfortunately, the TBDMS group was sensitive under these conditions. Therefore, the final **DAP1** route presented the Sonogashira coupling before 5'-alcohol protection. Once the alkyne TMS group is cleaved with Bu_4NF, the **DAP2** product is either reacted with TBDMSCl to yield **DAP1** or with $NaNO_2$ to transform it to **iG2**, which is then functionalized at the 5'-position in similar conditions to afford **iG1**.

These 6 ethynyl-substituted nucleobases constitute a relevant collection of synthetic intermediates for supramolecular chemistry. The rich and useful reactivity of the terminal triple bond, either through Sonogashira couplings or "click" cycloaddition reactions make these 6 compounds convenient synthons for the preparation of complex self-assembled systems. In this work, we wanted to couple these bases to a very simple π-conjugated diethynylenephenylene moiety so as to study self-association and self-recognition processes *via* hydrogen-bonding. For the synthesis of these π-extended nucleosides (**G**, **C**, **iG**, **iC**, **A** and **U**; see Scheme 3), iodoarene **1** was prepared first by Pd-catalyzed coupling between 4-*tert*butylphenylacetylene and 1,4-diiodobenzene, which was used in excess in order to maximize the yield of monosubstituted product. The common intermediate **1** was then coupled with the corresponding ethynyl-terminated base (**G1**, **C1**, **iG1**, **iC1**, **DAP1** and **U1**), to produce the final compounds, which were purified and characterized by ^1H NMR, ^{13}C NMR, UV-vis, MS and HR-MS techniques.[28]



Scheme 3. Synthesis of lipophilic nucleosides **G**, **C**, **iG**, **iC**, **A** and **U**.

Evaluation of Dimerization and Association Constants

In this work we were particularly interested in assessing and comparing different experimental techniques and data analysis methods in order to determine equilibrium constants as accurately as possible. For these monomer-dimer equilibria, ^{1}H NMR, absorption and emission spectroscopy techniques were considered. However, we found the last technique not very reliable or practical due to the need to normalize each spectra by the total amount of absorbed light during the dilution experiment and due to the fact that both nucleosides absorbed and emitted in the same regions (purine nucleosides absorption and emission features were only slightly red-shifted with respect to those of pyrimidine nucleosides). Hence, only ^{1}H NMR and UV-vis dilution and titration experiments were carried out.[28]

The chemical shift or absorbance data as a function of the concentration were then analyzed by different methods. For ^{1}H NMR data, the software *Equilibria*[48] was found to be particularly handy and useful for these simple dimerization and 1:1 binding models.[49] Besides, the 1:1 binding can be fitted considering as well the possibility of host dimerization (see below). It is, however, a program for local analysis, meaning that the shift experienced by each ^{1}H probe is analyzed independently. Some ^{1}H NMR host-guest binding data was also fitted with the Matlab® scripts developed by P. Thordarson[22] that offer the possibility of global fitting, meaning that several ^{1}H probes can be fitted simultaneously, thus enhancing the quality of the fitting procedure. For the analysis of the optical absorbance data, however, the software *ReactLab*™ *EQUILIBRIA*[51] was the most appropriate one, since the whole spectra are globally fitted and both host and guest nucleoside dimerizations can be included in the fitting as competitive processes to the binding between nucleobase pairs.

Evaluation of Dimerization Constants (K_{dim}). Before studying the binding events between complementary bases, we were interested to ascertain the extent of H-bonding aggregation in each final π-conjugated nucleoside. Since we did not expect significantly strong self-association for any of the **G**, **C**, **iG**, **iC**, **A** or **U** products (i.e. $K_{dim} \leq 10^3$ M^{-1}), we devised a set of dilution experiments that were adjusted to a simple dimerization model. The formation of higher order aggregates was thus neglected at low concentrations.

The system equilibrium, the corresponding dimerization constant equation, and the mass balance are:

$$M + M \leftrightarrow M_2 \quad (1)$$
$$K_{dim} = [M_2]/[M]^2 \quad (2)$$
$$[M]_0 = 2\,[M_2] + [M] \quad (3)$$

where M is the corresponding π-conjugated nucleoside monomer. Hence, [M] can be expressed as a function of K_{dim} and $[M]_0$ as follows:

$$[M] = (-1 + (1 + 8\,K_{dim}[M]_0)^{1/2})/4K_{dim} \quad (4)$$

The chemical shifts for the relevant nuclei (δ_{obs}) or absorbance values at a given wavelength (A_{obs}) are described as a weighted average of the individual species:

$$\delta_{obs} = \delta_M\,([M]/[M]_0) + \delta_{M2}\,(2[M_2]/[M]_0) \quad (5)$$
$$A_{obs} = A_M\,([M]/[M]_0) + A_{M2}\,(2[M_2]/[M]_0) \quad (6)$$

The chemical shift and absorbance data as a function of total concentration were then analyzed by the different methods that have to deal with 3 unknown parameters: δ_M (or A_M), δ_{M2} (or A_{M2}) and K_{dim}. The dimerization constants obtained by these two techniques are displayed in Table 1. A representative example for both ^{1}H NMR and UV-vis concentration-dependent experiments and binding isotherms is given in Figure 2, but all of them can be found in the Supporting Information.[28]

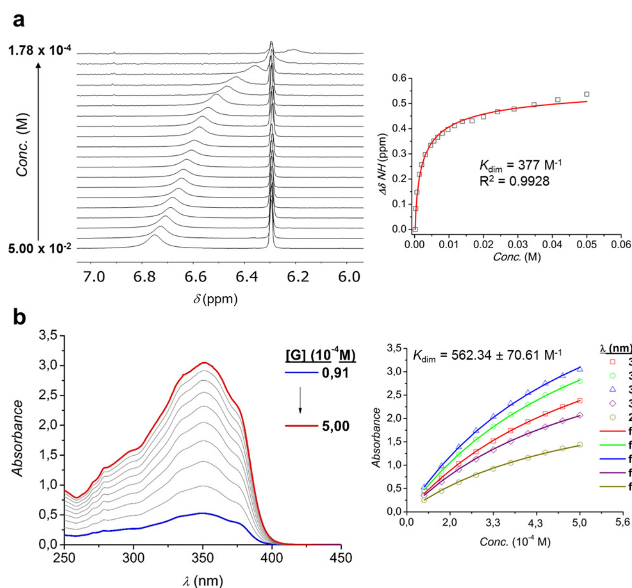


Figure 2. Selected regions of the (**a**) ^{1}H NMR and (**b**) absorption spectra as a function of **G** concentration showing the spectral changes occurring upon self-association. Right: fitting of the (**a**) **G** amide proton chemical shift or (**b**) absorption changes at 5 different wavelengths to a dimerization model.

Due to the low degree of self-association of our lipophilic nucleosides in chloroform, the equilibrium constants obtained from ^{1}H NMR experiments were found to be, in general, more reliable than those derived from absorption experiments. In the latter, a lower concentration must be used, which produced

Table 1. Dimerization (K_{dim}) and association (K_a) constants calculated by ^{1}H NMR or UV-vis titration experiments with the different lipophilic nucleosides prepared in this work.

GUEST \ HOST	G	C	A	U	iG	iC
G	400 [a,c] 550 ± 100 [a,e]	27800 [a,c] 28200 ± 100 [a,d] 15500 ± 400 [a,e]				12000 ± 1200 [a,e]
C	29000 [a,c] 6100 ± 50 [a,d,51] 2790 ± 700 [a,e]	250 [a,c] 30 ± 5 [a,e]			20100 ± 500 [a,e]	
A			4 [a,c] 10 [b,c]	300 [a,c] 200 ± 10 [a,d] 3300 [b,c] 2300 ± 20 [b,d]		
U			250 [a,c] 200 ± 20 [a,d] 2700 [b,c] 2200 ± 30 [b,d] 1400 ± 150 [b,e]	20 [a,c] 40 [b,c]		
iG		31000 [a,c] 22800 ± 100 [a,d] 42700 ± 2000 [a,e]			900 ± 150 [a,e]	22600 ± 300 [a,e]
iC	13700 [a,c] 19700 ± 50 [a,d] 17200 ± 1300 [a,e]				46200 ± 1300 [a,e]	150 ± 10 [a,e]

[a] In $CHCl_3$ (or $CDCl_3$). [b] In $CHCl_3$ (or $CDCl_3$):CCl_4 (2:3). [c] NMR data fitted with *Equilibria*[48] considering host dimerization. [d] NMR data fitted with the Matlab® scripts developed by P. Thordarson[22]. [e] UV-vis absorption data fitted with *ReactLab*™ EQUILIBRIA.[51]

binding isotherms that mainly covered a region of low probability of binding (p). That is especially evident in the case of the nucleosides with lower dimerization constants (i.e. **U** and nucleosides, the dimerization constants were also evaluated in the less polar $CHCl_3$ (or $CDCl_3$):CCl_4 (2:3) solvent system, which produced a higher degree of self-association. Nevertheless, the dimerization constants obtained by both techniques are in the same order of magnitude and consistent with literature values.[23-27]

In the case of the novel **iG** and **iC** nucleobases, dimerization constants were found to relatively high, in the same order to those found for **G**. As a matter of fact, these products were not extraordinarily soluble in chloroform and their ^{1}H NMR spectra showed rather broad NH/NH_2 resonance peaks, which complicated the analysis by this technique at high concentrations. Dimerization constants were instead withdrawn from UV-vis dilution measurements in this case.

Evaluation of Association Constants between Complementary Nucleosides. Next, we performed titration experiments between complementary bases in order to determine their association constants (K_a). Increasing amounts of a solution of the guest nucleoside (G) were added over a solution of the complementary host nucleoside (H). The guest solutions contained as well the host nucleoside, so that [H] was not altered during titration. We arbitrarily assigned the purines (**G**, **iG**, **A**) as the hosts and the pyrimidine nucleosides (**C**, **iC**, and **U**) as guests, although we also performed and analyzed the opposite titration (see Table 1).

Only a 1:1 binding model was considered. In this case, the system equilibrium, the corresponding association constant equation, and the mass balance are:

$$H + G \leftrightarrow HG \quad (7)$$

$$K_a = [HG]/[H][G] \quad (8)$$

$$[G]_0 = [G] + [HG] + [G_2] \quad (9)$$

$$[H]_0 = [H] + [HG] + [H_2] \quad (10)$$

Notice that in the mass balance we also include the possibility of host and, in the absorption measurements, guest dimerization as a competitive reaction to host-guest binding. Hence, equations (1) and (2) were also considered in the analyses. The NMR probe on the host nucleoside has 3 chemical shifts corresponding to the species in solution: the unbound chemical shift (δ_H) the chemical shift of the complex with the guest (δ_{HG}) and the chemical shift the host dimer (δ_{H2}). The observed chemical shift will be a mixture of the 3 shifts according the mole fraction of each species present and can be calculated according to:

$$\delta_{obs} = (\delta_H[H] + \delta_{HG}[HG] + \delta_{H2}[H_2]) / ([H] + [HG] + 2[H_2]) \quad (11)$$

On the other hand, during the UV-vis titration experiments, the normalized absorbance value at a given wavelength (A_{obs}) can be described as:

$$A_{obs} = (A_H[H] + A_{HG}[HG] + A_{H2}[H_2] + A_{G2}[G_2]) / ([H] + [HG] + 2[H_2] + 2[G_2]) \quad (12)$$

A typical set of titration experiments is shown in Figure 3. The chemical shift and absorbance data as a function of guest concentration were then analyzed. As stated above, NMR titrations were fitted with the software *Equilibria*,[48] which offers the possibility of including host dimerization in the analysis, or, in some cases, with the Matlab® global fitting scripts developed by P. Thordarson,[22] which results in lower standard errors. UV-vis titrations were instead fitted with the software *ReactLab*™ *EQUILIBRIA*[51] that includes both the whole spectra, as well as host and guest dimerization constants in the analysis. The binding constants obtained are displayed in Table 1.

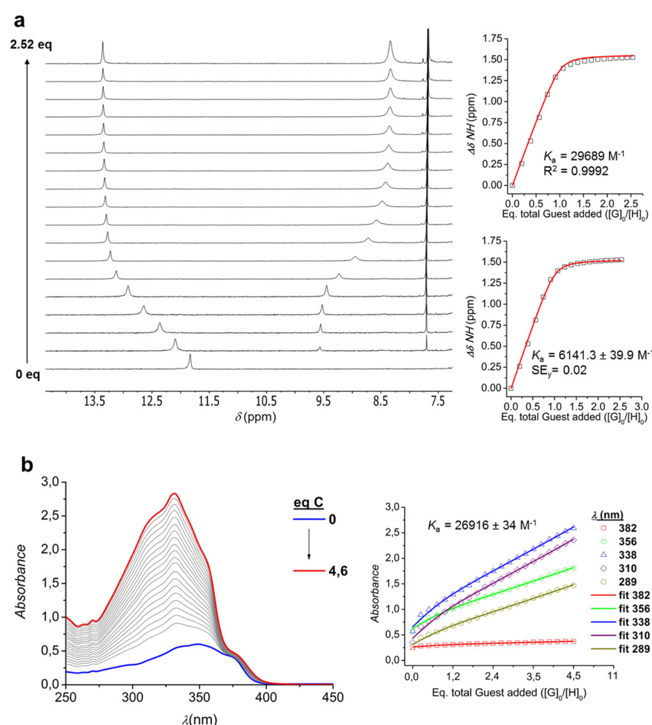


Figure 3. Selected regions of the (**a**) ^{1}H NMR and (**b**) absorption spectra obtained during the titration experiment of **G** (host) as a function of **C** (guest) concentration showing the spectral changes occurring upon association.[51] Right: fitting of the (**a**) ^{1}H chemical shift or (**b**) absorption changes at 5 different wavelengths to a 1:1 binding model.

Despite NMR and UV-vis titration experiments were performed employing two different techniques, concentration ranges and fitting programs, the 1:1 binding constants derived from these experiments are in reasonable agreement. In addition, the values obtained in the experiments where purines were considered as the hosts and pyrimidines as the guests are related to those acquired when the opposite titration order was applied (pyrimidines as hosts and purines as guests).

In the case of **G**-**C** or **A**-**U** base pairs, the association constants derived in this work match the values obtained by other authors (see Table 1).[23-27] Nucleosides **A** and **U**, having a symmetric ADA:DAD H-bonding pattern (Figure 4), associate in $CHCl_3$ (or $CDCl_3$) with K_a = 1.8–3.1 x 10^2 M^{-1}. In the less polar $CHCl_3$ (or $CDCl_3$):CCl_4 (2:3) solvent mixture the association constants were found to increase by an order of magnitude, reaching K_a = 1.4–3.2 x 10^3 M^{-1}. On the contrary, the binding constants calculated for the asymmetric DDA:AAD H-bonding patterns (Figure 4), found in **G**-**C**, **G**-**iC**, **iG**-**C** and **iG**-**iC** base pairs, are in the order of 10^4 M^{-1}. For instance, the binding constants obtained in $CHCl_3$ (or $CDCl_3$) amount to: K_a = 1.2–2.0 x 10^4 M^{-1} (**G**-**iC**), K_a = 1.5–3.0 x 10^4 M^{-1} (**G**-**C**),[51] K_a = 2.0–4.3 x 10^4 M^{-1} (**iG**-**C**), and K_a = 2.2–4.7 x 10^4 M^{-1} (**iG**-**iC**).

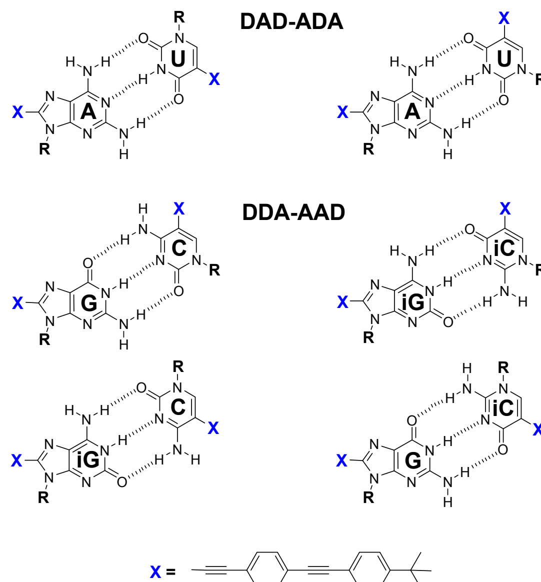


Figure 4. Triply H-bonded self-complementary base pair structures considered in this work.

Conclusions

In this work we have prepared a series of lipophilic nucleosides comprising natural and non-natural bases that are π-conjugated to a short oligophenylene-ethynylene fragment. These bases include guanosine, *iso*guanosine, 2-aminoadenosine as purine heterocycles, and cytidine, *iso*cytosine and uridine as complementary pyrimidine bases. The H-bonding dimerization and association processes between complementary bases were as well evaluated using different techniques (^{1}H NMR and absorption spectroscopies), solvents, concentration ranges and fitting programs. Symmetric ADA:DAD H-bonding patterns (**A**-**U** base pairs) produce 1:1 binding constants in the order of 10^2 M^{-1}, whereas asymmetric DDA:AAD H-bonding patterns (**G**-**C**, and the novel **G**-**iC**, **iG**-**C** and **iG**-**iC** base pairs) yield association constants in the order of 10^4 M^{-1}. This increase in two orders of magnitude is well-known in the literature and is caused by the establishment of stabilizing secondary H-bonding interactions in the DDA:AAD pairs.[52] Some of the molecules prepared in this work, for instance the halogenated and ethynylated nucleobases, can be regarded as a relevant collection of "supramolecular synthons" that may be useful in the field of chemical self-assembly. In this work we have just coupled a simple oligo(phenylene-ethynylene) unit, which is useful for further studies in our group,[53] but a wide diversity of functional units may in principle be attached to these nucleobases by means of metal-catalyzed cross-coupling reactions in order to direct their organization.

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Notes and references

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Electronic Supplementary Information (ESI) available: synthetic details, procedures and characterization data for all new compounds; ^{1}H NMR and UV-vis dilution, titration and fitting data. See DOI: 10.1039/b000000x/

1 See the special issue on the status of self-assembly at the beginning of the XXI century: *Science* 2002, **295**.

2 J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89.

3 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.

4 C. J. Pedersen, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1021.

5 T. Steiner, *Angew. Chem. Int. Ed.,* 2002, **41**, 48.

6 L. J. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.,* 2001, **40**, 2382.

7 D. González-Rodríguez and A. P. H. J. Schenning, *Chem. Mater.,* 2011, **23**, 310.

8 A. P. H. J. Schenning and D. González-Rodríguez in *Organic Nanomaterials*, T. Torres, G. Bottari (Eds.), John Wiley & Sons, Inc., Hoboken, New Jersey, 2013, pp 33.

9 R. P. Sijbesma and E. W. Meijer, *Chem. Commun.,* 2003, 5.

10 J. L. Sessler, C. M. Lawrence and J. Jayawickramarajah, *Chem. Soc. Rev.,* 2007, **36**, 314.

11 S. Sivakova and S. J. Rowan, *Chem. Soc. Rev.,* 2005, **34**, 9.

12 L. Brunsveld, B. J. B. Folmer, E.W. Meijer and R. P. Sijbesma, *Chem. Rev.,* 2001, **101**, 4071.

13 S. K. Yang and S. C. Zimmerman, *Isr. J. Chem.,* 2013, **53**, 511.

14 T. F. A. De Greef, M. M. J. Smulders, M. Wolffs, A. P. H. J. Schenning, R. P. Sijbesma and E. W. Meijer, *Chem. Rev.,* 2009, **109**, 5687.

15 S. Yagai, *J. Photochem.Photobiol. C: Photochem. Rev.,* 2006, **7**, 164.

16. P. Jonkheim, P. van der Schoot, A. P. H. J. Schenning and E. W. Meijer, *Science*, 2006, **313**, 80.

17 F. Würthner, Z. Chen, F. J. M. Hoeben, P. Osswald, C.-C. You, P. Jonkheim, J. van Herrikhuyzen, A. P. H. J. Schenning, P. P. A. M. van der Schoot, E. W. Meijer, E. H. A. Beckers, S. C. J. Meskers and R. A. J. Janssen, *J. Am. Chem. Soc.,* 2004, **126**, 10611.

18 S. Yagai, S. Mahesh, Y. Kikkawa, K. Unoike, T. Karatsu, A. Kitamura and A. Ajayaghosh, *Angew. Chem. Int. Ed.,* 2008, **47**, 4691.

19 B. A. Blight, C. A. Hunter, D. A. Leigh, H. McNab and P. I. T. Thomson, *Nature Chem.,* 2011, **3**, 244.

20 (a) P. G. A. Janssen, S. Jabbari-Farouji, M. Surin, X. Vila, J. C. Gielen, T. F. A. de Greef, M. R. J. Vos, P. H. H. Bomans, N. A. J. M. Sommerdijk, P. C. M. Christianen, P. Leclère, R. Lazzaroni, P. van der Schoot, E. W. Meijer and A. P. H. J. Schenning, *J. Am. Chem. Soc.,* 2007, **131***,* 1222. (b) P. G. A. Janssen, A. Ruiz-Carretero, D. González-Rodríguez, E. W. Meijer and A. P. H. J. Schenning, *Angew. Chem. Int. Ed.,* 2009, **48**, 8103.

21 (*a*) A. Gissot, K. Oumzil, A. Patwaab and P. Barthélémy, *New J. Chem.*, 2014, **38**, 5129. (*b*) V. Abet and R. Rodriguez, *New J. Chem.*, 2014, **38**, 5122.

22 P. Thordarson, *Chem. Soc. Rev.,* 2011, **40**, 1305.

23 W. L. Jorgensen and J. Pranata, *J. Am. Chem. Soc.,* 1990, **112**, 2008.

24 J. Sartorius and H.-J. Schneider, *Chem. Eur. J.,* 1996, **2**, 1446.

25 A. Dunger, H.-H. Limbach and Klaus Weisz, *J. Am. Chem. Soc.,* 2000, **122***,* 10109.

26 E. M. Todd, J. R. Quinn, T. Park and S. C. Zimmerman, *Isr. J. Chem.,* 2005, **45**, 381.

27 A. Likhitsup, R. J. Deeth, S. Otto and A. Marsh, *Org. Biomol. Chem.,* 2009, **7**, 2093.

28 See the Supporting Information for further details.

29 D. González-Rodríguez, J. L. J. van Dongen, M. Lutz, A. L. Spek, A. P. H. J. Schenning and E. W. Meijer, *Nature Chem.,* 2009, **1**, 151.

30 D. González-Rodríguez, P. G. A. Janssen, R. Martín-Rapún, I. De Cat, S. De Feyter, A. P. H. J. Schenning and E. W. Meijer, *J. Am. Chem. Soc.,* 2010, **132**, 4710.

31 B. Zhang, Z. Cui and L. Sun, *Org. Lett.,* 2001, **3**, 275.

32 Y. Xu, H. Jin, Z. Yang and L. Zhang, *Tetrahedron*, 2009, **65**, 5228.

33 I. Manet, L. Francini, S. Masiero, S. Pieraccini, G. P. Spada, and G. Gottarelli, *Helv. Chim. Acta*, 2001, **84**, 2096.

34 S. L. Forman, J. C. Fettinger, S. Pieraccini, G. Gottarelli and J. T. Davis, *J. Am. Chem. Soc.,* 2000, **122**, 4060.

35 M. S. Kaucher and J. T. Davis, *Tetrahedron Lett.,* 2006, **47**, 6381.

36 A. Holý, J. Günter, H. Dvoráková, M. Masojídková, G. Andrei, R. Snoeck, J. Balzarini and E. De Clercq, *J. Med. Chem.*, 1999, **42***,* 2064.

37 M. Bobek, I. Kavai, R. A. Sharma, S. Grill, G. Dutschman and Y.-C. Cheng. *J. Med. Chem.* 1987, **30**, 2154.

38 J. Asakura and M. J. Robins, *J. Org. Chem.* 1990, **55**, 4928.

39 A. Mayer, A. Häberli and C. Leumann, *Org. Biomol. Chem.,* 2005, **3**, 1653.

40 M. S. Amer, A. M. Amer, A. F. S. Ahmed and W. M. Farouk, *Indian J. Chem., Sect. B* 2001, **40B**, 382.

41 P. Lang, C. Gerez, D. Tritsch, M. Fontecave, J.-F. Biellmann and A. Burger, *Tetrahedron*, 2003, 7315.

42 R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874.

43 L. A. Agrofoglio, I. Gillaizeau and Y. Saito, *Chem. Rev.*, 2003, **103**, 1875.

44 E. C. Western and K. H. Shaughnessy, *J. Org. Chem.*, 2005, **70**, 6378.

45 A. Dumas and N. W. Luedtke. *Chem. Eur. J.*, 2012, **18**, 245.

46 Q. Gui-Rong, R. Bo, N. Hong-Ying, M. Zhi-Jie and G. Hai-Ming, *J. Org. Chem.*, 2008, **73**, 2450.

47 S. C. Jurczyk, J. T. Kodra, J.-H. Park, S. A. Benner and T. R. Battersby, *Helv. Quim. Acta,* 1999, **82**, 1005.

48 The *Equilibria* program was developed by Christopher Marjo, Mark Wainwright Analytical Centre, University of New South Wales, Sydney, Australia. http://www.sseau.unsw.edu.au/.

49 P. G. Young and K. A. Jolliffe, *Org. Biomol. Chem.*, 2012, **10**, 2664.

50 ReactLab™ EQUILIBRIA. Jplus Consulting Pty Ltd.

51 The low value obtained in the case of the **G**(host) + **C** (guest) titration analyzed by Matlab scripts (see Table 1) is probably due to the fact that this fitting method does not consider host (**G**) dimerization. In fact, when the same data was analyzed with *Equilibria* ignoring **G** dimerization, a value of K_a = 6564 M^{-1} was calculated.

52 W. L. Jorgensen and J. Pranata. *J. Am. Chem Soc.,* 1990, **112**, 2008.

53 C. Montoro-García, J. Camacho-García, A. M. López-Pérez, N. Bilbao, S. Romero-Pérez, M. J. Mayoral and D. González-Rodríguez, *Submitted*.