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Kévan Pérez de Carvasal, Gérard Vergoten, Jean-Jacques Vasseur, Michael Smietana, François Morvan. Supramolecular recognition of phosphodiester-based donor and acceptor oligomers forming gels in water. *Biomacromolecules*, 2023, 24 (2), pp.756-765. 10.1021/acs.biomac.2c01203 . hal-04120160

HAL Id: hal-04120160

<https://hal.science/hal-04120160>

Submitted on 7 Jun 2023

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Supramolecular recognition of phosphodiester-based donor and acceptor oligomers forming gels in water

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ABSTRACT: Inspired by automated DNA synthesis, electron-rich dialkoxynaphthalene (DAN) donor and electron-deficient naphthalene-tetracarboxylic diimide (NDI) acceptor phosphodiester-linked homohexamers were synthesized by the phosphoramidite method. Two types of hexamers were prepared, one with only one phosphodiester between the aromatics (i.e. DAN or NDI) and a second with two phosphodiesters around a propanediol between the aromatics leading to the latter more flexible and more hydrophilic hexamers. The folding properties of these homohexamers alone or mixed together, in water only, were studied by UV-Visible absorption spectroscopy and

atomic force microscopy (AFM). AFM imaging revealed that 1:1 mixture of hexaDAN and hexaNDI formed fibers by charge transfer donor acceptor recognition leading to a hydrogel after drying. The organization of the resulting structures is strongly dependent on the nature of the complementary partner leading to the formation of mono- or multi-layers hydrogel networks with different compactness.

INTRODUCTION

The choice of a solvent in supramolecular assemblies¹ is a crucial parameter as it influences the recognition, folding and assembly capacity of the chosen units. The physical properties of water (polarity, solvation, hydrogen-bonding) lead to important modifications of the recognition phenomena governed by effects that are absent in other solvents. Consequently, supramolecular chemistry in water is singular and often challenging.² Supramolecular systems compatible with water^{3,4} have attracted a lot of interest,⁵⁻⁷ and several studies increased the water solubility of large aromatic groups, with the introduction of charges⁸⁻¹⁰ or hydrophilic functions.¹¹⁻¹⁴ Nevertheless most studies relied on organic solvents such as methanol, ethanol and DMSO to help solubilize and organize their systems and only few supramolecular assemblies were investigated in saline aqueous media or in water only.¹⁵⁻²¹

Among the interactions that guide supramolecular assemblies, charge transfer (CT) interaction implying aromatic electron donors and aromatic electron acceptors has been widely used²² especially since it is generally intensified in water²³ and high polar protic solvents than in apolar solvents.²⁴⁻²⁶

Of the various supramolecular assemblies that can be generated from CT interactions, hydrogels²⁷ usually observed in AFM imaging as a xerogel after drying,²⁸⁻³⁰ are particularly interesting for their applications,^{31, 32} such as drug delivery systems,³³ antimicrobial agents for wounds³⁴ and matrix for bio-inspired artificial tissue engineering.³⁵ While there are many examples of hydrogen-bonded hydrogel networks,^{36, 37} only a few studies described the production of hydrogels through charge transfer interactions in aqueous media.³⁸⁻⁴³ CT interactions have many advantages providing not only self-assembly capacities but also recognition and selection properties.

We previously demonstrated that a negatively charged poly-phosphodiester heterohexamer, P(DN)₃P composed of alternating aromatic dialkoxynaphthalene (DAN, D) donors and aromatic naphthalene diimide (NDI, N) acceptors and having propanediol ending arms (P) (Scheme 1), was able to fold into nanotubes in water with lengths of 400 nm to 1 μm depending on maturation times and concentration.⁴⁴ This heterohexamer was obtained by solid-supported DNA synthesis,^{45, 46} from easily synthesized DAN and NDI phosphoramidite building blocks⁴⁴ (Fig.1A).

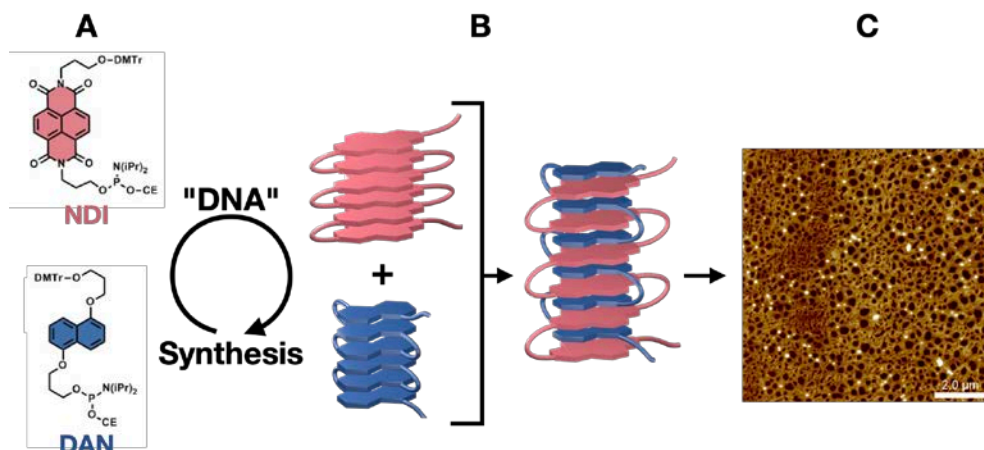


Figure 1. (A) Naphthalene diimide NDI and Dialkoxynaphthalene DAN phosphoramidite building blocks used for the synthesis of homohexamers with a DNA synthesizer, (B) Schematic representation of homohexamers assembly, (C) AFM imaging of the assembly depicted in (B) showing a network.

These results prompted us to investigate the duplex formation by CT interaction and the structuration of water-soluble homohexameric sequences composed of either DAN or NDI units linked by negatively charged phosphodiesteres.⁴⁷ We demonstrate here that either alone or mixed together, these negatively charged short oligomers are able to form in water nanotubes or fibers leading to hydrogels after drying.

EXPERIMENTAL SECTION

Oligomers synthesis. The solid-supported synthesis of oligonucleotides was performed on a 394 ABI DNA synthesizer. All conventional CPG columns, reagents and solvents for DNA synthesis were purchased from Link© technologies, ChemGenes© Corporation and Biosolve© Chimie. The oligomers were elongated from the propanediol solid support, at 1 μ mol scale, according to standard phosphoramidite chemistry protocols. The detritylation step was performed for 65 s using 3% TCA in CH_2Cl_2 . For the coupling step, benzylmercaptotetrazole (0.3 M in anhydrous CH_3CN) was used as the activator with 1, 2 or 3 phosphoramidites (0.1 M in CH_3CN , 3 min coupling time). The capping step was performed with acetic anhydride using commercially available solutions (Cap A: acetic anhydride:pyridine:THF 10:10:80 v/v/v and Cap

B: 10% N-methylimidazole in THF) for 10 s. The oxidation step was performed with a standard, iodine solution (0.1 M I₂, THF:pyridine:water 90:5:5, v/v/v) for 15 s. Oligomers were deprotected and released from the CPG by treatment with a solution of 7 N NH₃/MeOH for 24 h with orbital agitation. **WARNING:** Treatment with concentrated aqueous ammonia leads to degradations due to the opening of the imides of NDI. The CPG beads were first washed with dry MeOH then with water. The two methanolic fractions were pooled and dried on a speed vacuum then the water fraction was added and dried too.

HPLC. Crude oligomers were purified by reversed-phase C₁₈ HPLC (Macherey-Nagel, Nucleodur 250 x 10 mm, 5 μm) on a Thermo Fisher Ultimate 3000 system with a detector UV DAD 3000 at a flow rate of 4.5 mL/min. The conditions for the HPLC purification are reported in supplementary materials. The resulting oligomers with triethylammonium cations were exchanged on a DOWEX 50W X2 conditioned with Na⁺ cation affording oligomers as sodium form which are more soluble in water. Reversed-phase C₁₈ HPLC (Macherey-Nagel, Nucleodur 75x4,6 mm, 5 μm) analysis were performed on a Dionex Ultimate 3000 system with a detector UV DAD 3000 at a flow rate of 1 mL/min, with a gradient of 1% to 40% acetonitrile with 50 mM of TEAAc over 20 minutes.

Oligomers preparation and storage. The oligomers were stored dry at -20 °C to avoid structuration in water, then were dissolved at 0.1 mM in water to withdraw the needed number of nanomoles, this volume was then completed to 1 mL with water to obtain the needed concentration while the stock solution was reconditioned for storage. Then the solution was heated to 90 °C for 30 minutes, then cooled to 4 °C over 3 hours and kept at this temperature for 12 more hours.

Oligonucleotides characterization by MALDI-TOF. mass spectra were recorded on Axima© Assurance in negative mode, calibration was performed with a mixture of oligomers for reference, anthranilic acid was used as matrix. Oligomers (0.75 μ L) were mixed with 1 μ L of saturated solution of anthranilic acid in acetonitrile-water (1:1, v/v), this mixture was then deposited on a MALDI plate and dried.

UV-Visible study. UV-Vis spectra were recorded on a VARIAN© Cary 300 Bio UV-Vis spectrophotometer at 25 °C. All oligomers were dissolved at 15 μ M in 1 mL of water for spectra analysis in an UV tank with 1 cm of path-length. Oligomers were heated to 90 °C for 30 minutes and slowly cooled to 25 °C to allow an optimized association before analysis.

AFM imaging study. Atomic force microscopy analyses were recorded using Nanoscope on three instruments: MultiMode 8 (Quantitative nanomechanics QNM) equipped with nanoscope V electronics in peak force mode. Bruker Dimension 3100 equipped with nanoscope IIIa quadrex electronics in tapping mode. Nanoman 5 equipped with nanoscope V electronics in tapping mode. We used 300-rtespa and Rfesp-75 probes from Bruker with a tip radius of 5 nm. The mica substrates of highest grade V1 mica discs 15 mm (Ted Pella, Inc., with a R_q equal to 0.09 nm) were attached to a steel baseplate with carbon tape. For each analysis 40 μ L of the aqueous solution containing our oligomers were placed on a freshly cleaved mica surface and dried at room temperature for 30 minutes to 4 hours for the hydrogel structures in a laminar flow cabinet.

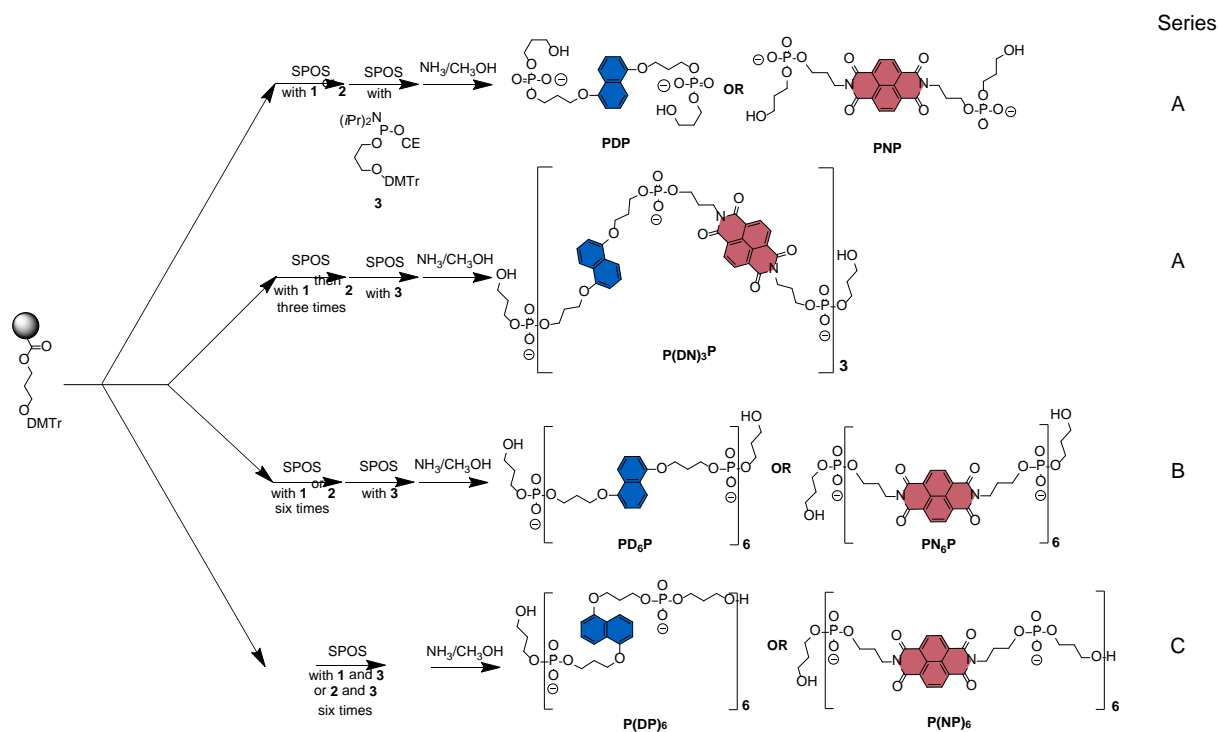
SEM imaging study. The study was performed on a FEI Quanta 200 FEG instrument from MEA platform, Université de Montpellier. The sample was deposited at 15 μ M on a carbon ribbon and dried for 2h before analysis.

Supramolecular assembly dissociation. For total dissociation of supramolecular assembly, a treatment with 5 mg of SDS (sodium dodecylsulfate) in a 2 mL solution at 90 °C is performed for 30 minutes. After that 200 μ L of a 2 M TEAAc buffer is added to the solution. The oligomer is then acquired using a C₁₈ Sep-Pak system from Waters.

Molecular modelling. The structure of the arrangements has been optimized using a classical Monte Carlo conformational searching procedure as described in the BOSS software.⁴⁸ For that purpose, the Spectroscopic Empirical Potential Energy function SPASIBA and the corresponding parameters are used^{49, 50} Molecular graphics and analysis were performed using the Discovery Studio 2020 Client software, Dassault Systemes Biovia Corp.

RESULTS AND DISCUSSION

Synthesis of monomers and hexamers of DAN and NDI. The homoheptamers were synthesized at a classic DNA scale synthesis of 1 μ mol using NDI (N), DAN (D) and propanediol (P) phosphoramidites starting from a propanediol solid support (Scheme 1, Fig. S1-4).⁴⁴ Three series of compounds were considered. The A series contains the monomers of DAN and NDI as PDP and PNP, and the alternated heterohexamer P(DN)₃P. They present at each end a propanediol phosphodiester moiety to increase their hydrosolubility. The B series concerns the homoheptamers having six DAN as PD₆P or six NDI as PN₆P. In the C series, designed to probe the influences of flexibility, an additional propanediol negatively charged phosphodiester unit was placed after each DAN or NDI leading to homoheptamers P(DP)₆ and P(NP)₆. Note that it also increased the number of negative charges and the global hydrophilicity of both heptamers.



Scheme 1 Synthesis of monomers and hexamers of DAN and NDI.

UV-Visible study. All hexaDANs PD_6P and $P(DP)_6$, and the monomer PDP showed similar UV-Vis spectral properties. The characteristic bands of the dialkoxynaphthalene moiety at 284, 296, 311 and 324 nm present a good resolution and are well defined and separated (Fig. 2A). In contrast when DANs are involved in a CT interaction, i.e. $P(DN)_3P$, the bands are smoothed which gives a broadened band around 300 nm. Note that the molar concentration of monomers is equal to that of $P(DN)_3P$ but is twice lower than the hexamers. So, no significant hypochromicity was observed for the hexamers. The hexaNDIs PN_6P and $P(NP)_6$ presented identical spectra with two bands at 363 and 386 nm, the latter being of lower intensity, while the

opposite is observed with the monomer (Fig.2B).^{8, 51-54} Finally, when NDIs are involved in a CT interaction (i.e. P(DN)₃P), a 37% hypochromicity was observed and both bands were broadened with a similar intensity, a slight red shift is also observable.⁴⁴ This variation of the NDIs bands intensities allowed to determine when NDI is monomeric, involved in a CT or in a stacked polyNDI interactions.^{14, 55}

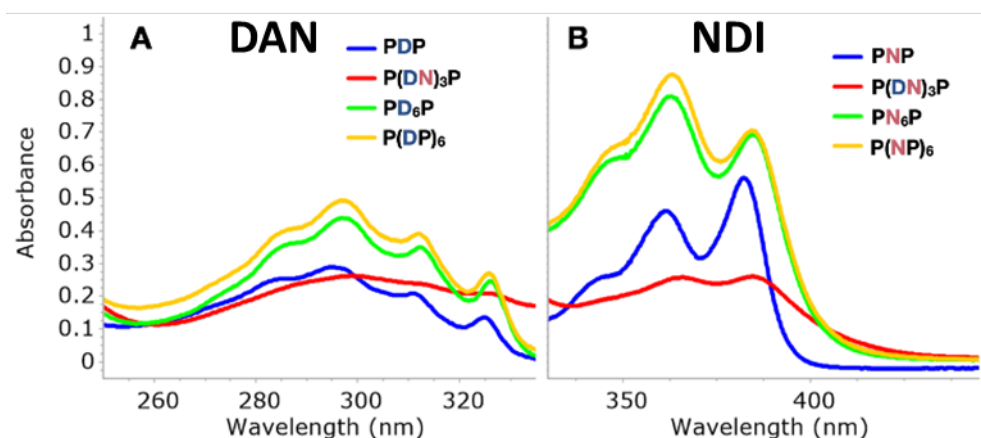


Figure 2. DAN (A) and NDI (B) based oligomers UV-Vis study in water, with PDP and PNP at 45 μ M, and P(DN)₃P, PD₆P, PN₆P, P(DP)₆, P(NP)₆ at 15 μ M.

We then studied the UV-Vis spectral properties of mixtures of homohexamers. The mixture of an equimolar quantity of a yellow solution of PN₆P with a colorless solution of PD₆P, instantly produced an intense pink solution visible to the naked-eye^{52, 56-59} characteristic of the CT interaction and confirmed by the low intensity band centered around 540 nm. The UV-Vis spectrum showed for the NDI bands a broadening as well as a hypochromicity and a similar intensity (Fig. 3A). These data support the strong interaction between DAN and NDI aromatic units resulting from their intertwining recognition.^{8, 53, 60}

In contrast, upon mixing an equimolar amount of P(DP)₆ and P(NP)₆, a weak-colored pink solution was observed as well as a faint CT band. In addition, NDI bands showed a stacked polyNDI pattern while DAN bands were unbroadened (Fig. 3B). These data suggest there was a weak or no intertwining between P(DP)₆ and P(NP)₆.

Both B and C series are composed of 6 aromatic units, but they differ by their number of negative charges (7 and 12, respectively). In addition, the higher hydrophilicity of the C series, demonstrated by the shorter retention time observed in RP HPLC analysis (Fig. S5), probably leads to a better solvation in water thus reducing the solvophobic effect. Consequently, the enhanced charge repulsion of the phosphodiester groups upon the mixing of C series hexamers, combined with a weak aromatic interaction and a higher entropic cost due to a higher flexibility, appears to have prevented strong intertwining of the aromatic units compared to the B series hexamers.

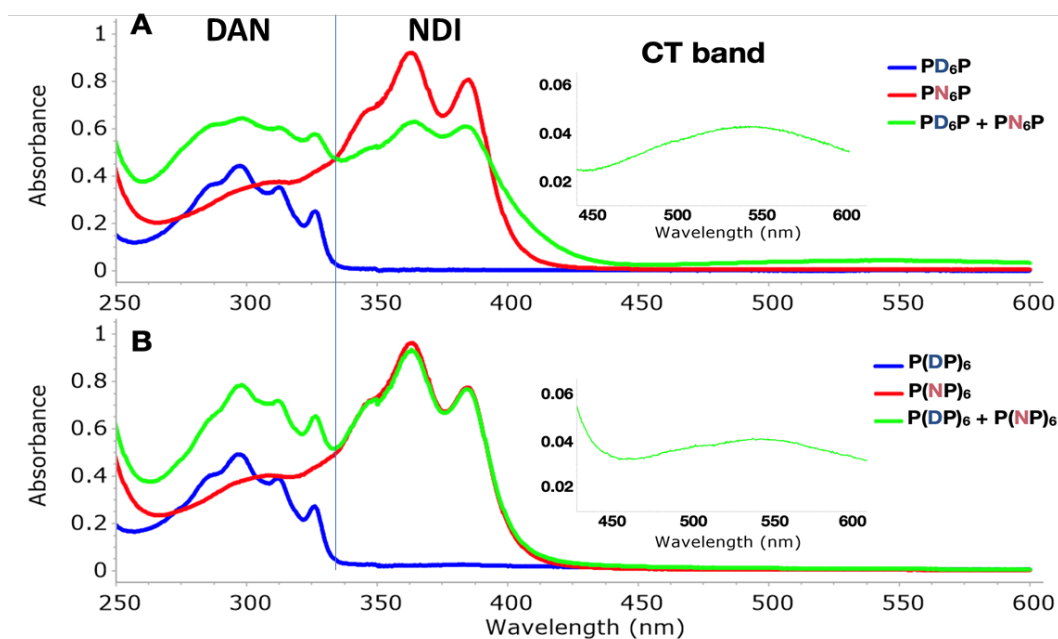


Figure 3. UV-Vis study at 15 μM in water of A) P(D)₆P, P(N)₆P, and their 1:1 mixture (inset zoom of CT band) and B) of P(DP)₆, P(NP)₆ and their 1:1 mixture (inset zoom of CT band at 30 μM .)

AFM study. Based on this observation, we hypothesized that supramolecular assemblies of a B-series mix would be denser than those of the C-series. To better understand these differences AFM imaging analyses were performed. TEM imaging cannot be performed because uranyl acetates induce a strong destabilization due to their high interaction with phosphodiester.⁶¹ Homoheptamers were studied alone in water at 15 μM after a heat-cooling gradient and 12-hour of maturation allowing a better organization than in our previous study. PD₆P presented only few and small linear fibers of 1 nm height and tens to hundreds nm long with a wideness of 40 to 100 nm, thus suggesting a connection of multiple fibers next to each other (Fig. 4A). Häner observed a similar fiber formation with phosphodiester heptapyrenes.⁶² By contrast, PN₆P, due to strong NDI interactions in water,²⁴ led to a large porous network of different heights ranging from 1 to 6 nm, suggesting up to six layers of 1 nm with hole disparity ranging from 20 to 280 nm in diameter (Fig. 4C). P(DP)₆ also showed few fibers similar to the one observed with PD₆P with a height of 1.5 nm (Fig.4B), while P(NP)₆ showed, after drying, a monolayer xerogel honeycomb network with holes ranging from 30 to 240 nm in diameter with a height of 1.5 nm (Fig.4D). Compared to PN₆P, the observed difference of structure can be explained by a better solvation of P(NP)₆ in water leading to a lower solvophobic effect.¹ The denser structuration observed with homoNDI hexamers in comparison with homoDAN₆ is a consequence of lower electronic repulsion and thus an enhanced interaction in water between acceptors units.¹

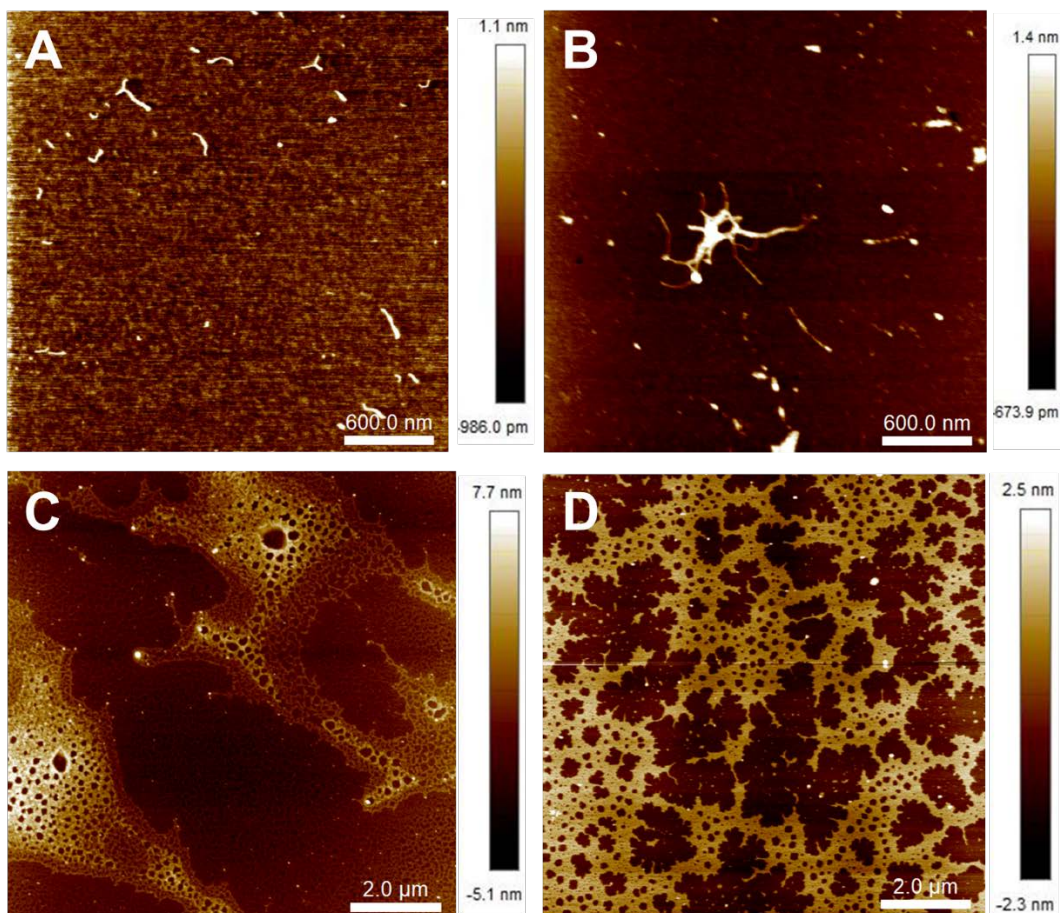


Figure 4. AFM images (height) at 15 μM in water of A) PD_6P , B) $\text{P}(\text{DP})_6$, C) PN_6P and D) $\text{P}(\text{NP})_6$.

We further investigated their structuring depending on the nature of a complementary partner, i.e. monomers or hexamers. First, each hexamer was mixed with its complementary monomer. Interestingly, a 1:6 mixture of PD_6P :PNP led to fibers of 400 to 900 nm in length, 22 nm wide and 1.2 nm in height (Fig. S6) and thus much longer than those observed with the hexamer alone. In contrast, a 1:6 mixture of $\text{P}(\text{DP})_6$:PNP showed an irregular sheet of 1 or 2 nm in height (Fig. S7). The addition of 6 equivalents of PDP to PN_6P or $\text{P}(\text{NP})_6$ gave for the former a dense and regular sheet 2 nm high (Fig. S8) and for the latter a more dispersed and irregular 3 nm high

sheet (Fig. S9). Thus, hydrophobic PD₆P and PN₆P hexamers formed structured nanotubes or a regular sheet assembly with their complementary monomers while the hydrophilic P(DP)₆ and P(NP)₆ hexamers led to more dispersed assemblies, probably due to a higher solvation in water leading to lower interactions.

Finally, all complementary hexamers were successively mixed together. The 1:1 mixture of the B and C series i.e. PD₆P:P(NP)₆ and PN₆P:P(DP)₆ led for the former to a dispersed and monolayered network averaging 1.6 nm high (Fig. 5A, S10) and for the latter a dense and monolayered network 2 nm high with hole disparity in the sheet ranging from 20 to 80 nm in diameter (Fig. 5B, S11).

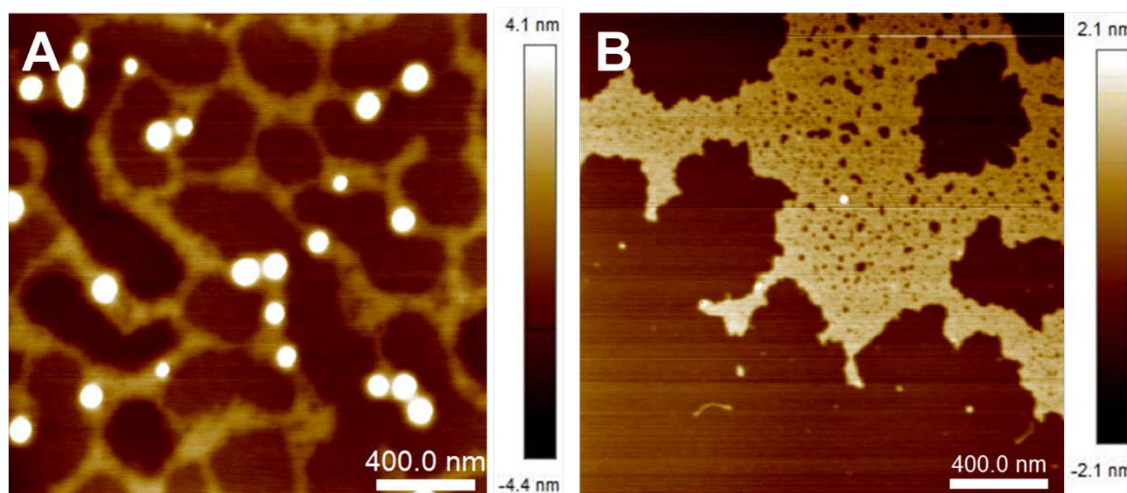


Figure 5. AFM images (height) in water of a 1:1 mixture at 15 μ M for each hexamers A) PD₆P:P(NP)₆ and B) PN₆P:P(DP)₆.

Mixing an equimolar amount of PD₆P with PN₆P (Fig. 6A) revealed a dense and large porous honeycomb network 20 nm high, with holes ranging from 30 nm to 450 nm in diameter. The recognition between DAN and NDI motifs of these more hydrophobic hexamers allowed a homogenous structure resulting from the aggregation of the fibers (Fig. S13). It should also be noted that while the drying usually takes place within minutes, this sample required hours (Table S1), thus indicating a better retention of water in the holes of the network.

Then, mixing an equimolar amount of P(DP)₆ and P(NP)₆ led to a monolayer dendrimer network 2 nm high (Fig. 6B). This structure is characterized by a wideness ranging from 150 to 300 nm and is narrower than that the one obtained with P(NP)₆ alone thus confirming the recognition of both complementary hexamers.

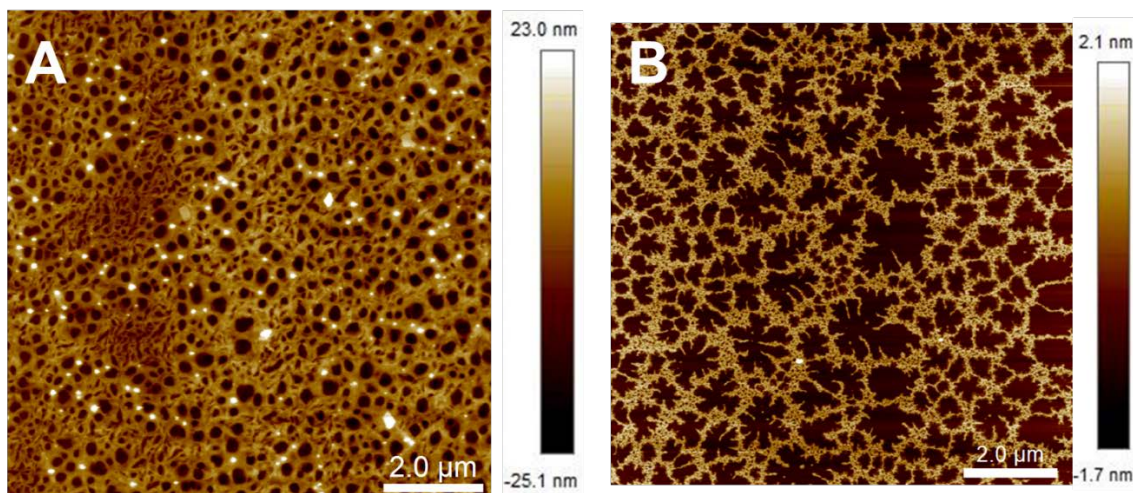


Figure 6. AFM images (height) in water of a 1:1 mixture at 15 μM for each hexamer of A) PD₆P:PN₆P and B) P(DP)₆:P(NP)₆.

As expected, the difference in the number of charges of the four mixtures led to four different systems. Indeed, the system with the most negative charge $P(DP)_6:P(NP)_6$ was also the most spread out because of the greater repulsion between the primary fibers, while the one with the least negative charges PN_6P and PD_6P showed the densest network. Another possibility to explain the lower efficiency of $P(NP)_6$ to recognize its complementary hexaDAN could be the formation of an anion- π pair between the NDI and the phosphodiester anion leading to a lower interaction with DAN moieties. Indeed, Matile reported the formation of anion- π between NDI and enolate or nitroate.⁶³⁻⁶⁸ Such anion- π interaction induced the formation of a CT band at 500 nm.⁶⁹ So, each hexaNDI was carefully studied by UV-visible spectroscopy at 15 μ M at 4 and 80 °C. For each, the band at 363 nm was higher than that at 386 nm in agreement with the π - π stacking of NDIs and no CT band was visible around 500 nm that allowed us to exclude the formation of an anion- π interaction between NDI and phosphodiesters (Fig. S12).

Compared to the nanotubes formed with alternating DAN and NDI units such as $P(DN)_3P$ ⁴⁴ the mixture of homohexamers led to the formation of hydrogels from longer fibers interacting with each other (Fig. S13), and trapping water at the same time.⁷⁰

The weak structural differences between $P(DN)_3P$ and PN_6P/PD_6P duplexes puzzled us as we anticipated that they would organize similarly. In fact, the conditions of the formation of the current structures in comparison with previously reported $P(DN)_3P$ were different. Indeed, in our first study the foldamer was dissolved in water at 25 °C and then kept overnight at 4 °C. In the current study the samples were dissolved in water, heated at 90 °C for 30 minutes, cooled to 4 °C over 3 hours (0.5 °C/min) and then kept at 4 °C overnight. So as a control $P(DN)_3P$ was treated as

the same way and AFM images showed the formation of a monolayer hydrogel 2 nm high with a high density (Fig. 7).

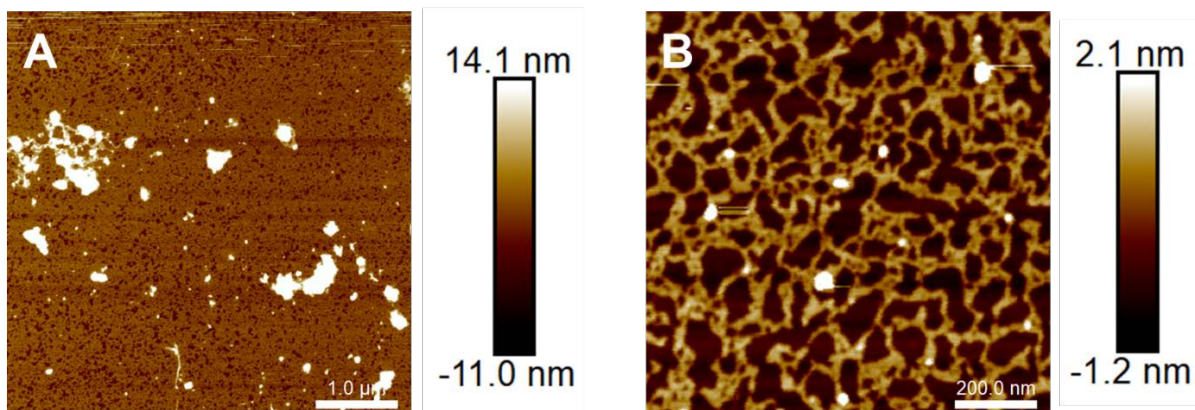


Figure 7. AFM images (height) in water of P(DN)₃P at 15 μM prepared with a gradient of temperature (90°C to 4°C over 3h) and kept at 4°C overnight A) 5 μm wide image, B) 2 μm wide image.

As a further control, both PN₆P and PD₆P hexamers were just dissolved in water together at 25°C and cooled at 4°C and kept overnight at this temperature. In this case, AFM images showed the formation of a hydrogel with partially few layers with a higher density than that of P(DN)₃P (Fig. 8). The difference of supramolecular arrangements according to the sample preparation has been previously reported by Häner.⁷¹

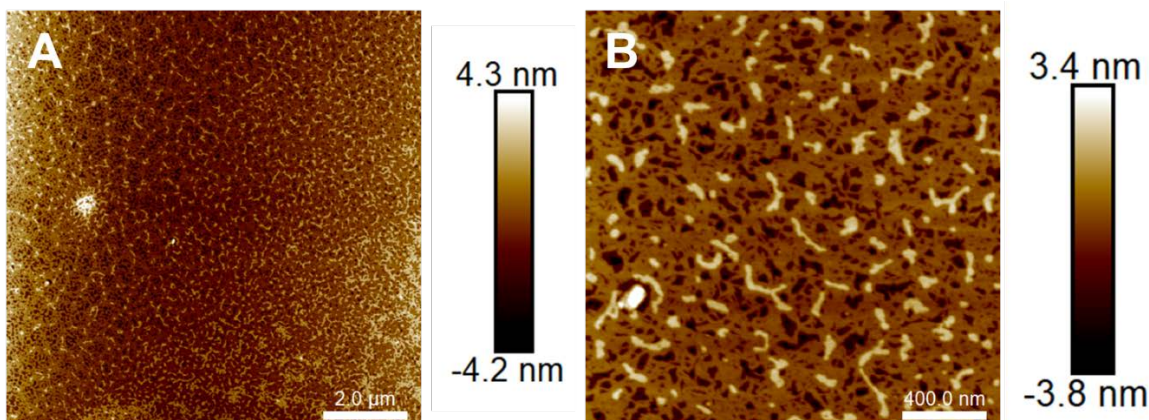


Figure 8. AFM images (height) in water of a 1:1 mixture at 15 μM of $\text{PD}_6\text{P}:\text{PN}_6\text{P}$ prepared at 25°C and then 4°C overnight.

So, we can assume that the alternated foldamer $\text{P}(\text{DN})_3\text{P}$ and the $\text{PN}_6\text{P}:\text{PD}_6\text{P}$ duplex are both able to form a hydrogel depending on the preparation of the samples. However, the formation of fibers or nanotubes leading to the hydrogel, after drying, might follow different ways (Fig. 9). For the alternated foldamer, the supramolecular arrangement may be weaker since the assembly of terminal DAN and NDI could be reversed by heating as we previously demonstrated.⁴⁴ In the case of the $\text{PN}_6\text{P}:\text{PD}_6\text{P}$ duplex, two types of arrangement can be foreseen. The first involves the formation of a blunt-ended duplex and a supramolecular arrangement driven by the assembly of terminal DAN and NDI units. The second implies the formation of long duplexes by concatenation of the hexamers. In the latter case the stability of the structure would be more stable. This difference of behavior may explain the differences of supramolecular arrangements observed with the formation of a hydrogel for the $\text{PN}_6\text{P}:\text{PD}_6\text{P}$ duplex independent of the conditions of preparation of the sample.

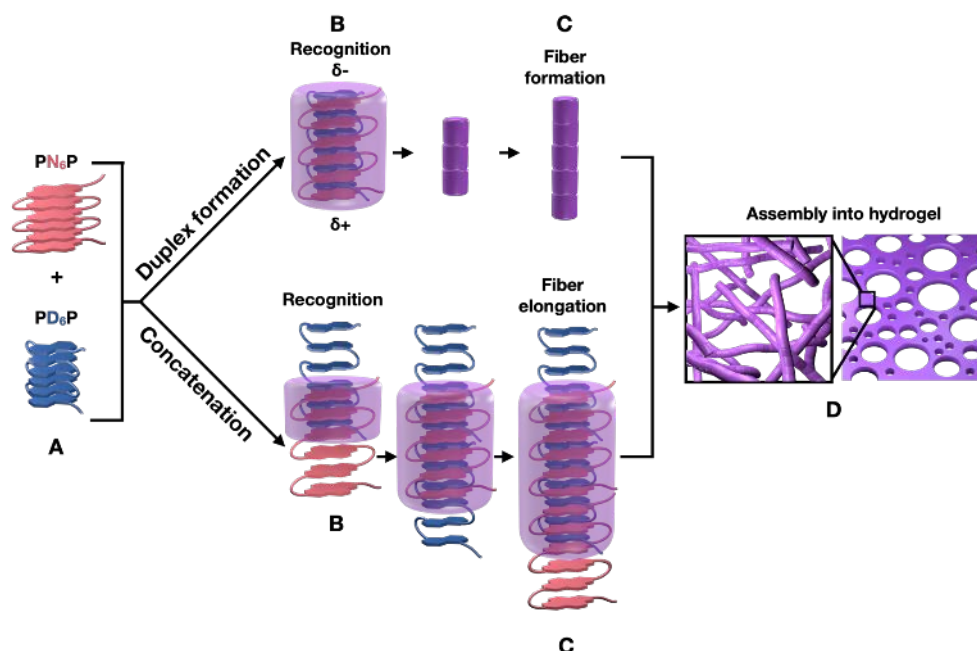


Figure 9. Illustration of the two ways the hexamers mixture is able to form a hydrogel by DAN/NDI recognition. A) Homohexamers mixture B) Foldamer intertwining C) Fiber formation and D) Hydrogel assembly.

Molecular modelling study. A molecular modelling study was performed to envision the arrangement of the homohexamers alone or as a duplex (Fig.S20-S28). For each structure, we calculated the average value of the distance between two phosphorus atoms on either side of an aromatic ring (PP) or between two central methylenes of the propanol linkers (CC), the distance between two aromatic units and the length of each structure (Table 1). HexaDANs stacked by π - π interactions led to DAN motifs in line with the phosphodiester groups on the sides. The distance between DANs is higher for P(DP)₆ (3.8 Å vs. 3.2 Å) probably due to its greater flexibility. While hexaNDIs also stacked by π - π interaction showed more regular structures with the same distance between NDIs (3.2 Å) probably due to the stronger NDI-NDI interaction. The molecular

modelling of duplexes showed DAN/NDI alternated structures similar to DNA duplexes with the aromatic motifs in the middle and the phosphodiesteres on the sides, and a distance between DAN and NDI ranging from 3.4 to 3.8 Å. The PP and CC distances of duplex are slightly lower than for the hexamers alone due to the stretching by the insertion of the DAN and NDI motifs to form alternated structures. The structure of the duplexes formed by recognition of complementary DAN and NDI is similar to that observed for the alternated foldamer P(DN)₃P with similar PP distances but the duplexes show less compact structures with a higher distance between DAN and NDI.

Table 1 Average distances between phosphorous atoms (PP), central methylenes (CC) and DAN or NDI aromatic motifs (arom/arom) and length of the different hexamers alone or in duplex.

Structures	Distance in Å					
	PP _{DAN}	CC _{DAN}	PP _{NDI}	CC _{NDI}	arom/arom	Length
PD ₆ P	15.0				3.2	19.0
P(DP) ₆		20.1			3.8	19.9
PN ₆ P			16.3		3.2	17.8
P(NP) ₆				21.4	3.2	17.8
P(DP) ₆ /PN ₆ P		15.1	15.7		3.7	38.7
PD ₆ P/P(NP) ₆	14.5			17.8	3.4	36.4
PD ₆ P/PN ₆ P	14.6		15.8		3.8	38.7
P(DP) ₆ /P(NP) ₆		16.4		20.4	3.6	39.3
P(DN) ₃ P	14.4		15.8		3.2	16.1

In figure 10, for the PN₆P/PD₆P duplex, only three NDI and DAN motifs are shown for ease of comparison (Fig. S25). The duplex shows a very similar arrangement compared to the hetero foldamer with a distance between two aromatics of about 3.5 Å and a width of about 1.6 nm wide.

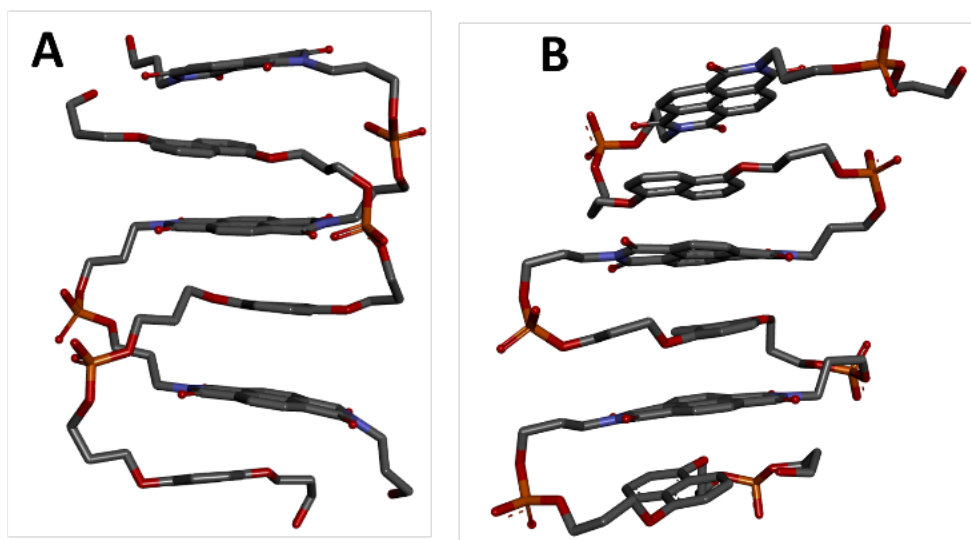


Figure 10 Modelling of the assembly of A) PD₆P/PN₆P, only three NDI and DAN motifs are shown for ease of comparison with B) P(DN)₃P.

CONCLUSIONS

In summary, phosphodiester-based homohexamers of DAN and NDI were easily synthesized by solid-supported DNA synthesis. By recognition of DAN and NDI motifs, the homohexamers were able to bind in water by charge transfer interaction exhibiting a CT band at 540 nm of low

intensity. In addition, we showed that the behavior of the two NDI motif bands at 363 and 386 nm is also a signature of the recognition with the DAN motif. A large variety of structures could be obtained from these hexamers from the formation of nanotubes to various types of hydrogel networks after drying. While additional negative charges in the hexamers increase their water solubility, they also influence their structuring in a detrimental way. From a simplistic point of view, the lowest association strength was observed for the hexamers that exhibited the best solvation in water due to excess of charge repulsion and a lower solvophobic effect. In addition, the introduction of additional charge is associated with a higher flexibility inducing a higher entropic cost. The less hydrophilic PD₆P:PN₆P mixture formed a dense and thick honeycomb hydrogel of 20 nm in height while the more hydrophilic mixes of hexamers formed irregular monolayer networks 2-3 nm in height. A SEM study of 1 : 1 mixture of PN₆P:PD₆P showed the formation of supramolecular fibrillar polymers in agreement with the formation of gels (Fig S29). These results demonstrate the delicate balance between water solubility, flexibility and lipophilicity for the assembly by recognition of supramolecular structures such as nanotubes and hydrogels. Hydrogels and water-soluble gel networks are currently being extensively studied for their use as biocompatible materials. Hydrogels formed with DNA are largely reported in the literature.^{72, 73} Usually, these hydrogels are formed by hybridization of DNA Y-shaped structures or DNA-grafted polymers with a complementary DNA sequence leading to a network. In the current hydrogels, we showed that short sequences with only six units are able to form hydrogels by supramolecular arrangement strongly stabilized by CT of the DAN and NDI pairs. Since these are the first charge transfer stabilized oligomers to yield a hydrogel in water, these new data shed new light in this area, further expanding the field of hydrogels formed by CT

recognition in water. However, additional studies will be carried out to better understand the behavior of this new supramolecular arrangements in water.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

HPLC profiles and MALDI-TOF spectra of hexamers. AFM images and molecular modeling of duplexes.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

K. Pérez de Carvasal thanks the University of Montpellier (UM) for the award of a research studentship. F. Morvan is a member of Inserm. We thank Dr David Canevet (University of Angers) for critical discussion. We thank Dr. F. Menges (University of Konstanz) for the use of Spectragryph software. We thank the Centrale de Technologie en Micro et nanoélectronique of UM for AFM analyses and F. Fernandez from the MEA platform, Université de Montpellier, for the SEM experiments.

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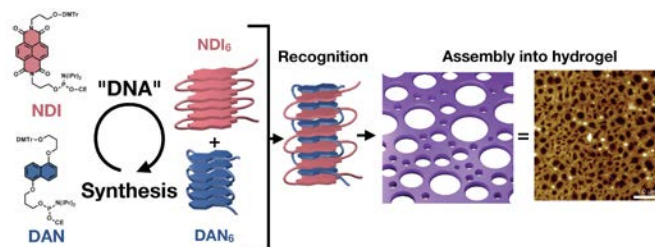
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SYNOPSIS.

Supramolecular recognition of phosphodiester-based donor and acceptor oligomers forming gels in water

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Duplexes of DNA-inspired homo-hexamers of the aromatic donor DAN and acceptor NDI form nanotubes or fibers by recognition and charge transfer interactions leading to a hydrogel after drying.