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Pyrene-functionalized Foldamer: Structural Impact and Recognition Properties Supported by Donor-Acceptor Interactions

F. Aparicio,[a] L. Faour,[a] M. Allain,[a] D. Canevet,[a,*] M. Sallé[a,*]

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An electroactive and luminescent foldamer based on an oligopyridine biscarboxamide skeleton was synthesized and characterised. Its conformation in the solid state proved to be strongly affected by the peripheral pyrene units. The latter also endow the target derivative with recognition abilities toward electron-withdrawing molecules, which allow for tuning the spectroscopic properties of the foldamer.

In order to understand and mimic biological functions, huge efforts are currently devoted to the study of synthetic compounds that can adopt well-defined organizations in terms of secondary and tertiary structures.[1–7] Important progresses have notably been reported with artificial foldamers,[8] which can be defined as oligomers that are able to adopt a well-defined secondary structure stabilized by non-covalent interactions. These elegant structures have already allowed outstanding achievements in research fields as different as HIV treatment,[9] drug delivery,[10] catalysis[11,12] or molecular machinery.[13–16] All these discoveries lie on the rich supramolecular chemistry of foldamers and, more particularly, helical foldamers. The latter are very appealing chemical entities since the modification of their primary structure allows for *i)* tuning the number of loops[17] and their hybridization ability (foldamers can form double, triple or quadruple helices),[18–20] ii) inducing a desired handedness,[21,22] and iii) modulating the volume, the shape and the surface potential of the cavity formed upon folding. Therefore, it is possible to adapt the primary structure of a given foldamer to enhance its hosting ability, in other words, to increase both the binding constant and the selectivity towards a target guest. Supramolecular chemists have shown that artificial foldamers can act as powerful and selective hosts for both ionic and neutral species.[3,23] Regarding the latter category, most examples belong to the carbohydrate and aminoacid families but other derivatives (fullerenes, carbamates, halogen-based derivatives, amines, carboxylic acids, alcohols, monoterpenes…) also proved to interact with specific foldamers.[1,2,24,25] Whatever the guest under consideration, the recognition process occurs inside the loop of the foldamer or over it.

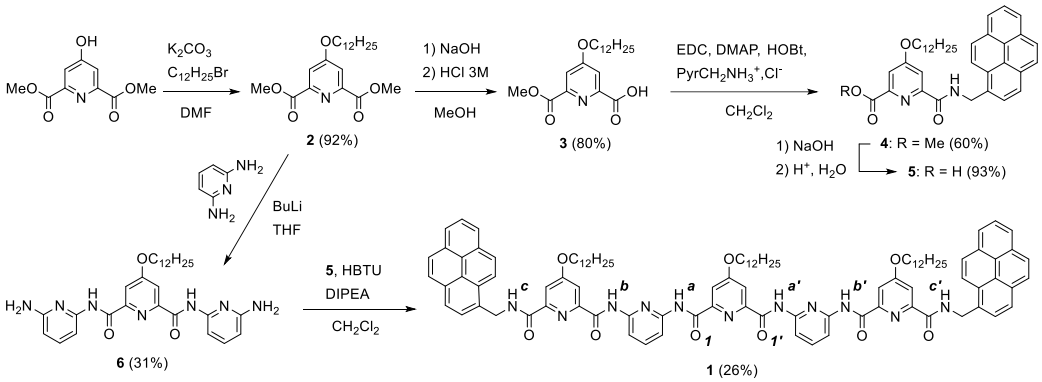
Herein, we propose a new strategy, which consists in grafting pyrenyl recognition units at the terminal positions of an oligomeric skeleton in order *i)* to favour the formation of a complex between a foldamer host and an electron poor aromatic guest, supported by donor-acceptor (D-A) interactions, *ii)* to evaluate the impact of the recognition process over the helical backbone, *iii)* and to take advantage of the electron-donating properties of pyrene to probe the recognition process.

To do so, oligopyridine-biscarboxamide foldamer frameworks, mostly developed by Huc, Lehn and coworkers,[18,26] were selected given their ability to form helical structures, the well-documented literature on the topic and the reasonable number of synthetic steps associated.

The synthesis of target compound **1** (Scheme 1 and SI file) involved six steps from dimethyl 4-hydroxypyridine-2,6-dicarboxylate,[27] following standard procedures except for two of them, which needed a special attention. A first delicate step lied on the preparation and isolation of monoacid **3**, which failed in our hands when adapting the procedures reported in the literature with the decyloxy analogue.[28] Consequently, a silica gel chromatography (eluent: CH_2Cl_2/MeOH 95/5 (*v/v*)) was led on the crude before acidification, and allowed for the straightforward isolation of the corresponding sodium carboxylate. Subsequent protonation yielded **3** in a reproducible manner (80%). Another critical step lied on the peptide-like coupling between carboxylic acid **5** with amine **6** in the presence of N,N-diisopropylethylamine (DIPEA) and *o*-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluoro-phosphate (HBTU) affording target foldamer **1** (26%).

[a] *Laboratoire MOLTECH-Anjou, Université d'Angers, 2 Bd Lavoisier, 49045 ANGERS Cedex. Emails: david.canevet@univ-angers.fr; marc.salle@univ-angers.fr*

Electronic Supplementary Information (ESI) available: Experimental details, ^{1}H and ^{13}C NMR spectra, infrared absorption and mass spectrometry information, ^{1}H NOESY experiments, crystal structures and UV-vis, emission and cyclic voltammetry experiments. See DOI: 10.1039/x0xx00000x



Scheme 1 Synthetic scheme of foldamer **1**.

The chemical structures of all new derivatives **1-6** were confirmed through standard analytical techniques (SI file). These analyses notably allowed for the detection of dimer $(\mathbf{1})_2$ by MALDI-TOF mass spectrometry (Fig. S1). This assessment is in line with previous observations on oligopyridine-biscarboxamide-based foldamers, which may hybridize to form double helices.[26,28,29] The formation of a dimer was further confirmed by X-ray diffraction analysis on monocrystals obtained from hexane vapor diffusion onto a chloroform solution (Fig. 1, S2-3, movie S1).

As usual with such oligoamide backbones,[18,26] intramolecular hydrogen bonds exist between the protons of the amide functions and the nitrogen atoms of neighbouring pyridyl rings (Fig. S2). However, the dimer does not adopt a double helix shape but rather crystallizes in an unprecedented conformation which is governed by the pyrene platforms. The O_1 oxygen atom (Scheme 1) is engaged in intermolecular hydrogen bonds with H_b and H_c atoms of the second strand (and by symmetry, $O_{1'}$ interacts with $H_{b'}$ and $H_{c'}$ atoms) (Fig. S3). On the other hand, the classical double helix conformation is in this case sacrificed in favor of intermolecular π–π interactions between both pyrene platforms of a first molecule and the central sandwiched pyridine unit of the second one (Fig. 1 and S3). Such a tweezer-like behavior results from donor-acceptor interactions between pyrene and pyridine biscarboxamide units which act as electron donor[30] and acceptor[31] respectively. Similar interactions have already been observed in the literature but not in a tweezer-like organization.[32]

As previously reported with analogous derivatives,[17,28,29] two sets of signals exist in the ^{1}H NMR spectrum (1 mM, $CDCl_3$, 298 K). To get additional insight, a dilution experiment was led in the same solvent from 100 mM to 0.2 mM (Fig. 2 and S4), confirming the occurrence of a slow equilibrium at the NMR timescale (300 MHz). In concentrated conditions, above 3 mM, a single set of proton resonances was observed and corresponded to the dimer $(\mathbf{1})_2$. Upon dilution, some signals decreased in intensity (*e.g.* 10.8 ppm), while new ones appeared at 10.1, 8.6 and 8.1 ppm for instance. The ^{1}H NMR spectrum of pure monomer **1** could not be reached upon dilution, even at 0.2 mM, which underlines the high stability of the dimer $(\mathbf{1})_2$ in chloroform. Plotting the evolution of monomer concentration as a function of the total concentration, resulted in a non-sigmoidal curve (Fig. S4), which allowed for determining the dimerization constant in chloroform, K_{dim}= 854 ± 52 (293 K). This value is relatively high in comparison to previously reported oligomers of similar lengths (see compound S1 in Scheme S1),[28] and illustrates the key role of pyrene terminal group in strengthening intermolecular interactions within the dimer.‡ The strong binding between both strands was also verified by measuring the ^{1}H NMR spectra of foldamer **1** in different solvents, namely toluene-d_8, *o*-dichlorobenzene-d_4, tetrahydrofurane-d_8 and pyridine-d_5 (Fig. S5). Whatever the solvent under

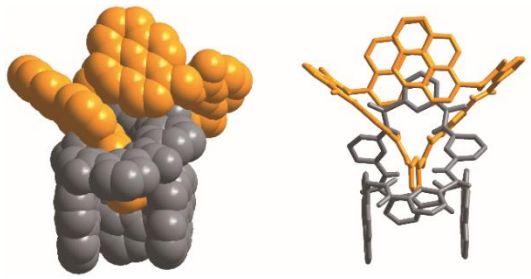


Fig. 1 X-ray crystal structure of compound **1** in its dimerised form $(\mathbf{1})_2$ (alkyl chains omitted for clarity).

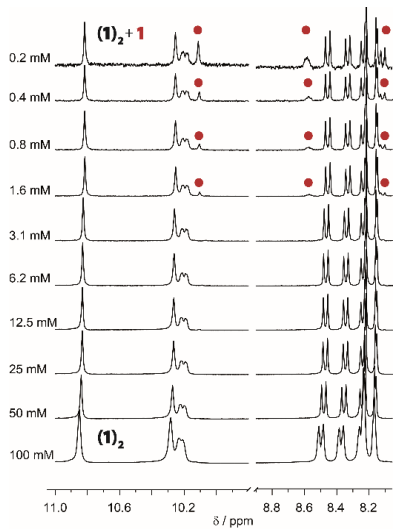


Fig. 2 Partial ^{1}H NMR spectra of compound **1** upon dilution in $CDCl_3$. Monomer signals are labelled by red circles.

consideration, compound **1** (2 mM) was mostly under its hybridized form, especially when decreasing solvent polarity: in toluene, the monomer form was hardly detected while clearly identified in tetrahydrofuran or pyridine, the latter being a particularly competitive solvent with the hybridization process.[19,26,33]

Altogether, these observations underline the impact of peripheral pyrene units, which are not only responsible for the obtaining of an unusual dimer, but also contribute to an increased stability of the latter.

Given its electron-rich nature, pyrene has been widely used as a π-donating unit in the context of molecular materials,[30] whereas the pyridyl-2,6-biscarboxamide fragment displays a moderate electrodeficient character (A), justifying the occurrence of donor-acceptor (D-A) interactions between both groups.[34] We therefore explored this ability to promote D-A interactions by opposing compound **1** to various π-accepting guests and by evaluating the impact of such recognition events over the hybridization process. To do so, different planar π-acceptors were selected, namely anthraquinone, dicyanobenzene and fluorene-based acceptor **7** (Fig. 3). Keeping constant the concentration of compound **1** (1.5 mM, $CDCl_3$, 293 K), a large excess of anthraquinone (10 eq.) or 1,4-dicyanobenzene (40 eq.) was added. These additions did not result in any significant modification of the ^{1}H NMR spectrum of foldamer **1** (Fig. S6) and did not promote any color change either. On the contrary, upon addition of increasing amounts of the yellow-colored compound **7** (Fig. 3b), which is a strong π-accepting molecule as confirmed by cyclic voltammetry experiments (Fig. S7), the initially colorless solution of foldamer **1** turned green (Fig. 3d), characterizing a charge transfer transition. In addition, significant changes were observed by ^{1}H NMR spectroscopy of monomer **1** and dimer $\mathbf{1}_2$ signals (Fig. 3a and S8) and showed that the corresponding equilibrium was progressively shifted towards the monomeric form up to four equivalents of acceptor (*i.e.* from *ca* [**1**]/[$\mathbf{1}_2$] ≈ 3/7 in the absence of **7** to [**1**]/[$\mathbf{1}_2$] ≈ 7/3 with 4 equivalents of **7**). In addition, and as previously reported in the literature,[5] the shielding of dimer signals (*e.g.* from 10.84 ppm to 10.74 ppm), which was also observed upon diluting **1** (Fig. 2), is associated to conformational changes required for dehybridization. As for monomer signals, their chemical shifts also underwent variations (*e.g.* from 10.12 ppm to 10.39 ppm), resulting from the donor acceptor association formed between **7** and **1**. ^{1}H NMR spectra revealed that this charge-transfer complex was in fast exchange at the NMR timescale (300 MHz) and led to significant modifications of the chemical shifts of **7** (Fig. 3a), which are independent from concentration (Fig. S9).

The 1:1 stoichiometry of the complex was determined through Job plot analysis (^{1}H NMR– Fig. 3c and Fig. S10) and further confirmed by MALDI-TOF mass spectrometry (Fig. S11).

The relative intensities of dimer and monomer signals (in slow exchange) together with the deshielding of the monomer signal (fast exchange between monomeric **1** and D-A association **1·7**) allowed for determining the respective concentrations of free **1**, dimer $(\mathbf{1})_2$ and complex **1·7** (Fig. 4 and S12), affording equilibrium constants $K_{D\text{-}A}$ and K of 277 ± 16 and 90 ± 10, respectively ($CDCl_3$, 293 K).[9]

A key added value linked to the incorporation of pyrene units lies on their remarkable fluorescent properties, which may contribute to probe the intermolecular interactions.[35,36] Pyrene can indeed return to the ground state through monomer, excimer or sometimes exciplex emissions after excitation.[37] As mentioned above, the solution of foldamer **1** (1.5 mM, $CDCl_3$) turns green upon addition of acceptor **7** (Fig. 3d). Therefore, we studied the evolution of the absorption and emission properties in the presence of acceptor **7**.

The addition of increasing amounts of **7** onto a chloroform solution of foldamer **1** (1.5 mM) provoked the progressive appearance of a large charge-transfer band on the absorption spectrum, from 540 to 850 nm,[38] where both foldamer **1** and **7** do not absorb (Fig. 5a and S13).[§] Excitation of compound **1** at 316 nm resulted in a large emission band spread from 390 to 600 nm, which corresponds to an excimer-type emission, while acceptor **7** does not emit under these conditions.

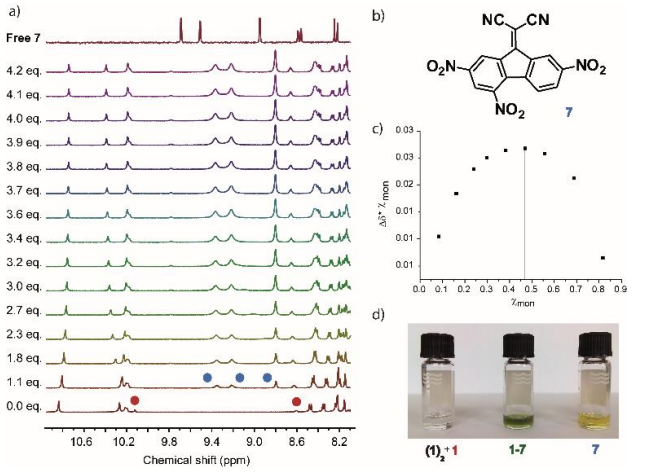


Fig. 3 (a) ^{1}H NMR spectra of compound **1** upon addition of increasing amounts of **7** in $CDCl_3$. Red circles are used for monomer signals **1** and blue circles for **7**. (b) Chemical structure of acceptor **7**. (c) Job plot experiment monitored by ^{1}H NMR spectroscopy with compounds **1** and **7** in $CDCl_3$ (C_T = 1.5 mM). (d) Color change observed upon mixing compounds **1** and **7** in $CHCl_3$.

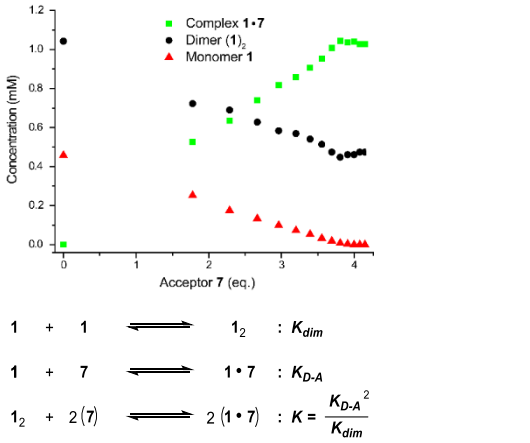


Fig. 4 *Top*. Evolution of the concentrations of free monomer **1**, charge transfer complex **1·7** and dimer $(\mathbf{1})_2$ depending on the number of equivalents of acceptor **7** ([**1**] = 1.5 mM, $CDCl_3$, 293 K). *Bottom*. Equilibria under consideration

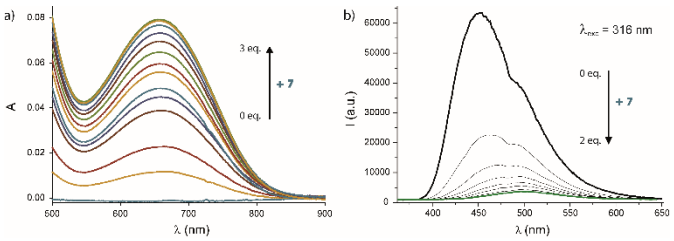


Fig. 5 Evolution of the UV-vis absorption (*left, l* = 0.1 cm) and emission (*right*) spectra of **1** (1.5 mM) upon addition of **7** in $CHCl_3$ at 298 K.

Upon addition of **7**, the luminescence of foldamer **1** was gradually quenched up to two equivalents of acceptor (Fig. 5b). The Stern–Volmer plot obtained by using the experimentally determined values of fluorescence intensities in the absence (I_o) and presence (I) of quencher **7** was found to be nonlinear, showing positive curvature (Fig. S14). This positive curvature and the saturation observed at two equivalents indicates that quenching is not purely due to collisional or dynamic quenching and reveals a static quenching process attributed to the formation of the donor-acceptor association **1·7**.[14-16]

Conclusions

In summary, an electroactive and luminescent oligopyridine bis(carboxamide) foldamer was synthesized and characterized. The introduction of electron-donating pyrene units proved to affect both the hybridization process with an increased dimerization constant and the structure of the dimer, which adopts an unprecedented conformation, as shown through X-ray diffraction study. Among different planar π-acceptors, foldamer **1** showed a good affinity towards fluorenone derivative **7** and its spectroscopic properties could be tuned by addition of the latter. To our knowledge, this example constitutes the first foldamer displaying hosting abilities thanks to π-donor-π-acceptor interactions. Currently, our efforts focus on foldamers functionalized with alternative electro/photo-active units, exploring their unique spatial organization for recognition processes.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ For instance, a double helix was observed in deuterated chloroform at 298 K with an equilibrium constant of K'_{dim}= 210 for an analogous oligoamide derivative of **1**, despite the presence of five alkoxy chains that are known for favoring dimerization.[28]

§ At lower wavelengths, the large molar extinction coefficients of foldamer **1** and **7** and their respective concentrations did not allow for measuring the absorption spectrum. At lower concentrations, the charge transfer complex could not be observed because of the moderate K and $K_{D\text{-}A}$ equilibrium constants (Figure S13).

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