Heteromeric double helix formation by cross-hybridization of chloro-and fluoro-substituted quinoline oligoamides†

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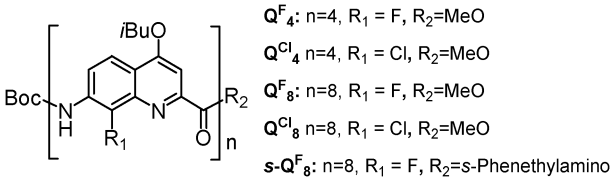
Oligoamides of 8-chloroquinoline have been synthesized and shown to assemble into double helical dimers both in solution and in the solid state, and to undergo cross-hybridization with 8-fluoroquinoline oligoamide analogues; the handedness of these double helices can be controlled *via* chiral residues.

Considerable progress has been achieved in the design and characterization of synthetic oligomers that hybridize into multiple helices based on non-natural hybridization motifs.[1] Prominent examples include metal coordination-based helicates,[2] aromatic oligoamides,[3] oligoresorcinols,[4] ethynylhelicene oligomers,[5] *m*-terphenyl backbone oligomers exploiting amidinium–carboxylate salt bridges,[6] alternate sequences of aromatic hydrogen-bond donors and acceptors.[7] Most of these systems however, consist of homodimeric double helices. Heteromeric double helices are less common,[2a,e,3e,4c,5b,6] despite the fact that they constitute more attractive targets since they might provide artificial molecular platforms to achieve information storage and duplication as in DNA. This scarcity reflects the difficulty to achieve reliable heterologous pairing modes between artificial molecular strands. In this respect, the aminidium–carboxylate pairing described by Yashima and Furusho represents a significant advance.[6]

As a part of our program aiming at investigating double helices of aromatic oligomers, we recently reported the synthesis, folding and hybridization of 8-fluoroquinoline oligoamides.[3g] Solid-state and solution studies demonstrated that octamer $\mathbf{Q^F_8}$ adopts helical conformations and assembles into an antiparallel double-helical homoduplex, with a dimerization constant $K_{dim} = 8.5 \times 10^5$ L mol^{-1} in $CDCl_3$ at 298 K. Tetrameric $\mathbf{Q^F_4}$ also assembles into double helices, albeit much less stable than $(\mathbf{Q^F_8})_2$, which further aggregate into a quadruply stranded structure.[3g]

Among other factors, these helical conformations are stabilized by intramolecular N–H···F hydrogen bonds and C=O···F repulsions between consecutive quinoline units of the sequence.[8] On the other hand, the extent to which other halogen atoms may act as hydrogen-bond acceptors has remained unclear.[9] Li *et al.* reported that chlorine atoms participate in the formation of five-membered N–H···Cl hydrogen-bonded rings in aromatic mono-amides.[10] Intrigued by the possibility to direct folding of an entire aromatic amide oligomer using N–H···Cl hydrogen bonds, we envisaged to replace fluorine atoms by chlorine atoms in position 8 of each ring of $\mathbf{Q^F_n}$ oligomers. We now report the synthesis, folding and aggregation properties of $\mathbf{Q^{Cl}_4}$ and $\mathbf{Q^{Cl}_8}$. We find that $\mathbf{Q^{Cl}_8}$ hybridizes into double helical homodimers similar to $(\mathbf{Q^F_8})_2$, that $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^F_8}$ undergo cross-hybridization to form a heterodimer, and that helical handedness of these duplexes can be induced by means of a terminal chiral residue.

8-Chloroquinoline oligoamides were synthesized according to procedures similar to those used for their fluoro-counterparts and have been fully characterized (see ESI†). NMR studies of $\mathbf{Q^{Cl}_4}$ solutions compare well with those of $\mathbf{Q^F_4}$ and can be summarized as follows. ^{1}H NMR spectra are sharp and show strong downfield shifts of NH (amide) resonances of $\mathbf{Q^{Cl}_4}$ ($\delta > 11.5$ ppm, which is higher than in $\mathbf{Q^F_4}$) as well as spreading over a wide range ($\Delta\delta$ up to 0.5 ppm), consistent with their involvement in intramolecular hydrogen bonds (Fig. S1–S3†) and with a helically folded conformation. Concentration-dependent and variable-temperature NMR spectra suggest that $\mathbf{Q^{Cl}_4}$, like $\mathbf{Q^F_4}$, forms weak and labile aggregates in rapid exchange with the monomer on the NMR time scale (Fig. S2–S4†). No evidence was sought for regarding the exact nature of these aggregates.



The folding and aggregation behaviour of $\mathbf{Q^{Cl}_8}$ was able to be examined in more detail thanks to a solid-state structure (Fig. 1)‡ showing its hybridization into an antiparallel double helical dimer almost superimposable to the structure of $(\mathbf{Q^F_8})_2$ (Fig. S16†).[3g] The structure of $(\mathbf{Q^{Cl}_8})_2$ confirms the formation of N–H···Cl hydrogen bonds between adjacent quinolines of each strand. The average N–H···Cl distance in five-membered hydrogen bonded rings is 2.5 Å compared to 2.2 Å for N–H···F hydrogen bonds in $(\mathbf{Q^F_8})_2$. This difference appears to simply reflect the larger van der Waals radii of chlorine atoms and not a change in the curvature of the strand.

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† Electronic supplementary information (ESI) available: Synthetic procedures, experimental details and additional spectroscopic data. CCDC 745835. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b910435f

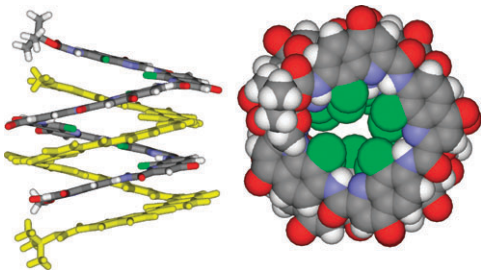

Fig. 1 Structure of $(\mathbf{Q^{Cl}_8})_2$ in the crystal. Isobutyl side chains and included solvent molecules have been omitted for clarity.

Another consequence of the larger size of chlorine is that in the inner hollow of the duplex is too small to accommodate any solvent or guest molecules.

Double helix formation in solution was supported by mass spectrometry (Fig. S13†) and by strong similarities with ^{1}H NMR spectra of $(\mathbf{Q^F_8})_2$ such as slightly broadened lines at room temperature and downfield shifted signals indicative of strong ring currents effects as can be expected for the duplex structure observed in the solid state. However, some differences were noted too. In particular, the ^{1}H spectra of $\mathbf{Q^{Cl}_8}$ in $CDCl_3$ and pyridine-d_5 show two sets of signals (Fig. 2, S6, S7†). This might have been interpreted as signals belonging to single and double helices in slow exchange as for $(\mathbf{Q^F_8})_2$ and $\mathbf{Q^F_8}$,[3g] but several facts disprove this interpretation: (i) except for the terminal methyl ester, the two sets of signals largely overlap whereas signals of single helices normally appear at lower field; (ii) proportions between the two sets of signals do not vary with concentration from 0.5 to 40 mM (Fig. S5†); (iii) upon heating to 52 °C in $CDCl_3$ and 47 °C in pyridine-d_5, the two sets of signals coalesce and rapidly split again upon cooling (Fig. 2, S6, S7†). The latter is incompatible with a single helix–double helix equilibrium of an octamer, for which equilibrium remains slow on the NMR time scale and even sometimes on the chromatographic timescale (see below). The two sets of signals cannot either be assigned to parallel and antiparallel double helices as this would require strand dissociation and would not give rise to rapid equilibration. The most plausible explanation appears to be the existence of isomeric forms of $(\mathbf{Q^{Cl}_8})_2$ that equilibrate through the sliding of one strand with respect to the other through a screw-like motion, as has been observed in pyridinecarboxamide oligomers.[3a] Remarkably, diluting or heating did not give rise to any signal that could be assigned to single helical $\mathbf{Q^{Cl}_8}$ (Fig. S6, S7†). The K_{dim} value of $\mathbf{Q^{Cl}_8}$ appears to be too high to measure using NMR even at high temperatures in solvents less favourable to hybridization such as pyridine-d_5. Chlorine substituents thus make $(\mathbf{Q^{Cl}_8})_2$ at least 10 to 100 times more stable than $(\mathbf{Q^F_8})_2$. Such stable aromatic duplexes have been encountered in one other series.[3i]

Since $\mathbf{Q^F_8}$ and $\mathbf{Q^{Cl}_8}$ both form stable and structurally similar double helices, we decided to investigate possible heterohybridization between them. When these compounds were mixed ^{1}H NMR spectra initially showed signals corresponding to $(\mathbf{Q^F_8})_2$ and $(\mathbf{Q^F_8})_2$ (Fig. 3(a)). Thus, cross-hybridization does not occur immediately, in contrast with other heteromeric double helices.[3e,6] Instead, the intensities of $(\mathbf{Q^{Cl}_8})_2$ and $(\mathbf{Q^F_8})_2$ signals slowly decreased and, concomitantly, one set of

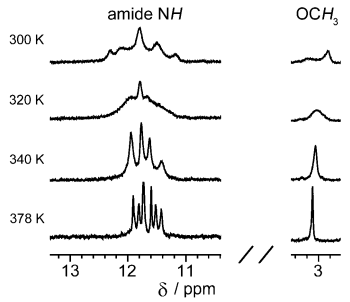

Fig. 2 Part of the temperature-dependent ^{1}H NMR spectra (300 MHz) of $\mathbf{Q^{Cl}_8}$ (1 mM) in pyridine-d_5 showing amide and methyl ester resonances.

new signals appeared suggesting the formation of a heterodimer $\mathbf{Q^{Cl}_8}\cdot\mathbf{Q^F_8}$. This assignment was confirmed by TLC, ESI and CD studies (*vide infra*). Signal multiplicity (two methyl ester peaks of equal intensities) indicates that this hybrid exists in only one form, like $(\mathbf{Q^F_8})_2$ and unlike $(\mathbf{Q^{Cl}_8})_2$, presumably an antiparallel double helix. In support to the fact that all species present are double helices is the observation that their proportions at equilibrium are concentration independent. Yet, the time needed to reach equilibrium does depend on concentration: *ca.* 300 h at 2 mM; 250 h at 4 mM, 150 h at 8 mM and 50 h at 50 mM (Fig. S11†). Most notably, the proportion of $\mathbf{Q^{Cl}_8}\cdot\mathbf{Q^F_8}$ at equilibrium represents 70%, above the 50% expected for a statistical distribution of $\mathbf{Q^F_8}$ and $\mathbf{Q^{Cl}_8}$ among the various duplexes (Fig. 3(f)). A possible reason for this preference might be steric complementarity between F and Cl atoms in the double helix hollow, as occurs between side chains in leucine zippers.

An equilibrated mixture of $(\mathbf{Q^F_8})_2$ and $(\mathbf{Q^{Cl}_8})_2$ was subjected to thin layer chromatography (TLC). As shown in Fig. 4, a new spot was observed between those of $(\mathbf{Q^F_8})_2$ (R_f 0.1) and $(\mathbf{Q^{Cl}_8})_2$ (R_f 0.9) assignable to $\mathbf{Q^F_8}\cdot\mathbf{Q^{Cl}_8}$ (R_f 0.45). The separation of these three species by TLC is illustrative of their kinetic stability: exchange with single helices is minor at the TLC time scale.[3j] The formation of $\mathbf{Q^F_8}\cdot\mathbf{Q^{Cl}_8}$ was also evidenced by high-resolution electrospray ionization mass spectrometry (ESI MS). Indeed, spectra of an equilibrated mixture of $(\mathbf{Q^F_8})_2$ and $(\mathbf{Q^F_8})_2$ show peaks that could be assigned to the three double helices, all as doubly charged species, according to their m/z values and their isotopic distribution (Fig. 4 and S12†).

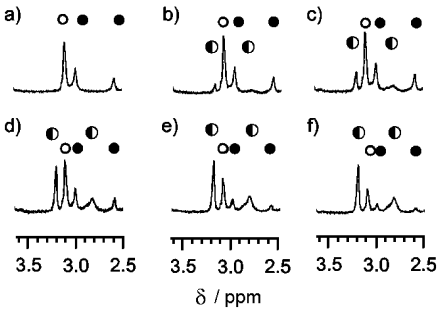

Fig. 3 Part of 400 MHz ^{1}H NMR spectra at 296 K showing methyl ester resonances at different time intervals after mixing $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^F_8}$ (8 mM each): (a) 0 h, (b) 12 h, (c) 28 h, (d) 70 h, (e) 118 h, (f) 155 h. Solid, empty and half filled circles show signals assigned to $(\mathbf{Q^{Cl}_8})_2$, $(\mathbf{Q^F_8})_2$ and $\mathbf{Q^{Cl}_8}\cdot\mathbf{Q^F_8}$, respectively.

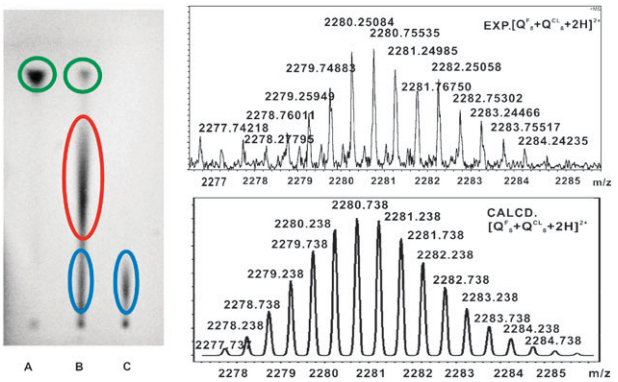

Fig. 4 Left: TLC on SiO_2 eluting with chloroform–ethyl acetate (95 : 5 v/v) showing the hetero-hybridization of $\mathbf{Q^{Cl}_8}$ and $\mathbf{Q^{F}_8}$. A: $\mathbf{Q^{Cl}_8}$; B: $\mathbf{Q^{Cl}_8}$ + $\mathbf{Q^{F}_8}$; C: $\mathbf{Q^{F}_8}$. Right: experimental (top) ESI MS and theoretical (bottom) isotopic distribution of hetero-double helix $[\mathbf{Q^{Cl}_8}{\cdot}\mathbf{Q^{F}_8} + \mathbf{2H}]^{2+}$.

Finally, the formation of hetero-double helices was further explored by circular dichroism (CD). Chiral octamer $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ was synthesized for this purpose (Scheme S3†). Variable-temperature ^{1}H NMR and high resolution ESI MS studies revealed that $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ forms double helices similar to that of $\mathbf{Q^{F}_8}$ (see ESI†). Additionally, CD spectroscopy shows that the chiral phenethylamine residue of $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ results in intense CD bands, suggesting $(\boldsymbol{S}\text{-}\mathbf{Q^{F}_8})_2$ has a preferred handedness which can tentatively be assigned to *P* helicity as in other *s*-phenethylamine-bearing oligoamides (Fig. 5 and S17†).[11] CD spectra of mixtures of $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ and $\mathbf{Q^{Cl}_8}$ were then measured while keeping the total concentration equal to 1×10^{-5} M. As shown in Fig. 5, CD intensities at 331 nm decreased when the proportion of non-chiral $\mathbf{Q^{Cl}_8}$ increased, but this decreases deviates positively from linearity. As expected, a linear relationship was found in the case of $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ and $\mathbf{Q^{F}_8}$, (data not shown). On the other hand, a solution of $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ was titrated with $\mathbf{Q^{F}_8}$ and $\mathbf{Q^{Cl}_8}$, respectively. The data show (Fig. S17 and S18†) that the CD intensity $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ at 331 nm follows a sigmoid increase upon adding $\mathbf{Q^{Cl}_8}$, however, it increases linearly upon adding $\mathbf{Q^{F}_8}$. These results are consistent with the preferred formation of heteromeric aggregates between $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ and $\mathbf{Q^{Cl}_8}$ possessing a preferred helix sense bias. The isosbestic point with $\Delta\varepsilon = 0$ at 305 nm and a Job plot derived from CD data (Fig. S15†) both support a 1 : 1 stoichiometry of this aggregate, consistent with a $\boldsymbol{S}$-$\mathbf{Q^{F}_8}{\cdot}\mathbf{Q^{Cl}_8}$ heteroduplex.

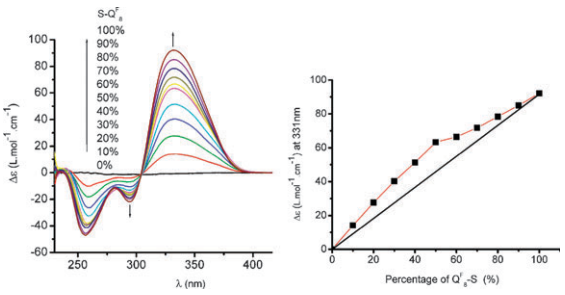

Fig. 5 CD spectra of mixtures of $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$ and $\mathbf{Q^{Cl}_8}$ in $CHCl_3$ at a fixed total concentration of 10^{-5} M. Solutions were equilibrated at 23 °C for 5 days before measurements. Right: plot of $\Delta\varepsilon$ values at 331 nm as a function of the proportion of $\boldsymbol{S}$-$\mathbf{Q^{F}_8}$.

In summary, we have shown that folding of aromatic oligoamides may be directed by N–H···Cl hydrogen bonds, that 8-chloroquinoline oligoamides hybridize into double helices and that these have a preference for cross-hybridization with their fluoro-quinoline counterparts. This preference may constitute the basis for a more refined heteromeric association based on steric complementarity.

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Notes and references

‡ *Crystal data*: $(C_{118}H_{114}Cl_8N_{16}O_{19})_2$, M = 4687.72, T = 173(2) K, monoclinic, space group $C2/c$, a = 31.428(6), b = 36.642(7), c = 24.101(5) Å, β = 114.01(3)°, V = 25353(9) Å^3, D_c = 1.228 g cm^{-3}, Z = 8, 56 066 reflections collected, 9628 independent reflections (R_{int} = 0.063), final R indices [$I > 2\sigma(I)$]: R_1 = 0.1389, wR_2 = 0.3449, R indices (all data) R_1 = 0.2104, wR_2 = 0.3872.

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