CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900877

A Self-Assembled Foldamer Capsule: Combining Single and Double Helical Segments in One Aromatic Amide Sequence

Chunyan Bao,[a] Quan Gan,[b] Brice Kauffmann,[a] Hua Jiang,*[b] and Ivan Huc*[a]

Abstract: In this manuscript, we present supramolecular capsules based on a new design relying on both self-assembly and folding of oligomeric strands. We have designed an aromatic amide foldamer in which each monomer encodes three levels of information: a specific cavity size, recognition groups for guest binding, and a propensity to adopt a single or a double helical motif. Thus, a tetradecameric sequence based on four different monomers was encoded so that a wide double helical segment resulting from the hybridization of two strands creates a cavity in which guests, such as 1,10-decanediol, can be bound. Additionally two narrow single helical segments form end-caps and isolate the guest from the solvent. The design, synthesis, solid-state and solution-state characterization of duplex formation and guest binding are presented.

Keywords: chirality · helical structures · molecular recognition · supramolecular chemistry · X-ray diffraction

Introduction

Self-assembly has proven to be an efficient method to produce large supramolecular containers endowed with molecular-recognition properties. Despite their large size, such containers can be based on remarkably simple molecular building blocks and often feature high levels of symmetry.[1–10] In contrast, Nature achieves highly selective molecular recognition using receptors that are primarily based on the *folding* of long and complex peptide sequences into well-defined conformations having low symmetry, if any. In this manuscript we present a synthetic receptor based on a combination of both folding and self-assembly of an oligomeric sequence, and describe the first synthetic host for organic guests having a double helical architecture.

Inspired by Nature's receptor design strategy, chemists have recently begun to explore the possibility to elicit molecular recognition within the cavities of oligomeric chains folded into single helices.[11–17] These objects have until now been much smaller and far less complex than proteic receptors. Nevertheless, they share with them a vast potential for tunability: they are based on sequences whose monomers can be changed one at a time and introduced by using the same synthetic methods. In principle, they are also amenable to larger and increasingly complex structures through the iterative elongation of their sequence. Along these lines, we have described helical capsules based on the folding of oligoamide sequences of various aromatic amino acids designed in order to create a large helix diameter at the center of the sequence and narrow diameters at the end, so as to define a closed space in which bound guest molecules are completely surrounded by the helix backbone.[17] A potential drawback of this design is that binding of an elongated guest would require a multiple turn helix comprised of numerous monomers: in other words, a difficult synthetic target. We assumed that a more straightforward route to helical containers having an elongated cavity may rest on the high propensity of some aromatic amide sequences to assemble into double-stranded helices twice as long as their single helical precursors.[18,19] As shown in the following, several potential hurdles had to be overcome to validate this concept, in particular the fact that none of these aromatic oligoamide double helices had been endowed with molecular recognition properties until now, and the fact that single helical seg-

[a] Dr. C. Bao, Dr. B. Kauffmann, Dr. I. Huc
Institut Européen de Chimie et Biologie
Université de Bordeaux–CNRS UMR5248 and UMS 3033
2 rue Robert Escarpit, 33607 Pessac (France)
Fax: (+33) 540-00-22-15
E-mail: i.huc@iecb.u-bordeaux.fr

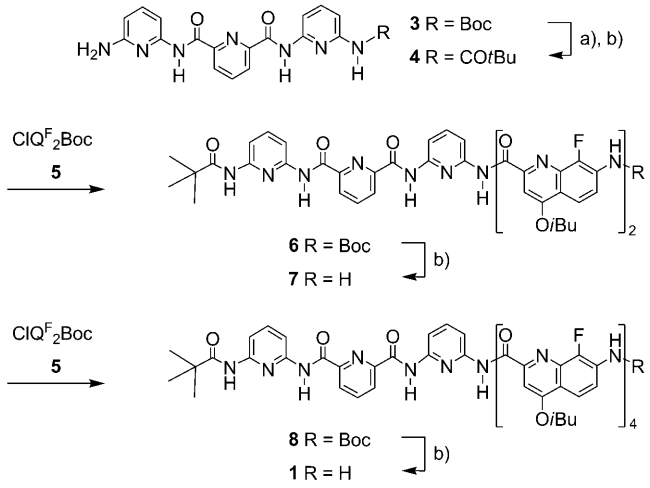
[b] Q. Gan, Prof. H. Jiang
Beijing National Laboratory for Molecular Sciences
CAS Key Laboratory of Photochemistry, Institute of Chemistry
Chinese Academy of Sciences, Beijing 100190 (China)
Fax: (+86) 10-82617315
E-mail: hjiang@iccas.ac.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900877.

ments and double helical segments had never been combined in a single foldamer sequence and shown to each adopt their preferred folded conformation independently from one another.

Results and Discussion

Design and synthesis: Oligomers **1** and **2** were designed as candidates for double helical receptor formation (Scheme 1). Both are based on the same set of monomers.

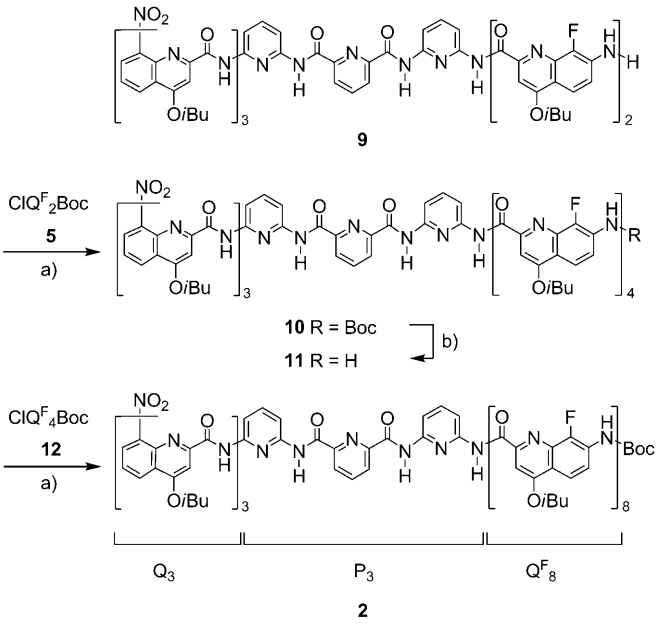


Scheme 1. Synthesis of $P_3Q^F_4$ **1**: a) pivaloyl chloride, DIEA, THF, 25 °C; b) TFA/DCM, 25 °C.

The longer sequence of **2** comprises a trimer of 8-amino-2-quinoline carboxylic acid (Q), known to form a helix too narrow to accommodate any guest and thus to cap the helix cavity.[20] Both **1** and **2** comprise a trimer of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid (P), which forms a helix with a polar hollow that binds to aliphatic hydroxyl or amino groups that can thus constitute hot spots to anchor guests within the helix cavity.[17] A tetrameric and an octameric amide sequence of 7-amino-8-fluoro-2-quinolinecarboxylic acid (Q^F) were also included in **1** and **2**, respectively. These oligomers fold into a helix the hollow of which is large enough to accommodate an alkyl chain, though it apparently does not engage in any attractive interactions with such moieties.[19]

Each segment of homologous monomer thus brings about a given helix diameter, and displays an array of functions that converge towards the helix hollow. In addition, the various monomers also differ in their preference for a single helical conformation or a hybridized double helix. Q_n oligomers do not hybridize into multiple helices.[20] P_n oligomers can hybridize, but not sequences as short as a trimer.[18] The terminal Q_3P_3 sequence of **2** was thus expected to preferentially form a single helix. However, Q^F oligomers form stable multiple helices; Boc-Q^F_4-OMe can form either antiparallel duplexes or quadruplexes, and Boc-Q^F_8-OMe has been shown to hybridize into an antiparallel double helix in solution and in the solid state ($K_{dim} = 8.5 \times 10^5\ L\,mol^{-1}$ at 25 °C in $CDCl_3$).[19] The shorter sequence of **1** (piv-$P_3Q^F_4$) and its Boc-protected precursor **8** (piv-$P_3Q^F_4$-Boc) were designed mainly as prototypes to assess whether a single P_3 and Q^F_4 segment would fold independently from each other. The longer sequence **2** (O_2N-$Q_3P_3Q^F_4$-Boc) was expected to possess all features required to form a double helical capsule.

The synthesis of **1** was achieved from monoamine mono-Boc-protected trimer **3** (Scheme 1). The amine group was coupled to pivaloyl chloride and the Boc group was subsequently removed with TFA to yield **4**. Coupling with the acid chloride of Q^F_2 afforded **6**, which was deprotected with TFA and subjected again to the acid chloride of Q^F_2 to give **8**, which was converted into **1**. The synthesis of **2** (Scheme 2)



Scheme 2. Synthesis of $Q_3P_3Q^F_8$ **1**. a) DIEA, THF, 25 °C; b) TFA/DCM, 25 °C.

was achieved from amine intermediate **9** ($Q_3P_3Q^F_2$) used in the preparation of the capsule $Q_3P_3Q^F_2A^FQ^F_2P_3Q_3$.[17a,21] We found that Q^F_n oligomers activated as acid chlorides could be smoothly added stepwise to extend the main chain, provided that n remained smaller than or equal to 4. Attempts to directly couple the acid chloride of Q^F_8 would have provided a more convergent route to **2** but all failed, presumably because of steric hindrance resulting from hybridization.

Hybridization of 1 and 2 into double helices: Unlike its precursor **8**, oligomer **1** could be crystallized and its solid-state structure solved by X-ray crystallography (Figure 1). The results show that two strands associate through the formation of an antiparallel double helix of two Q^F_4 segments. The terminal pyridine trimer P_3 of each strand sits on one end of

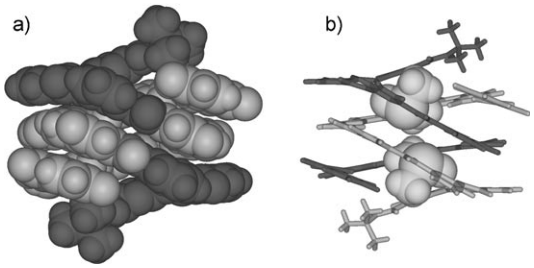


Figure 1. Structure of $(\mathbf{1})_2$ in the solid state. Isobutyl side chains, the included solvent molecules, and hydrogen atoms have been omitted for clarity. a) The CPK view shows the monomers coded as follows: P in dark gray and Q^F in light gray. The dark gray units belong to single helical-like (crescent) segments, whereas the light gray units belong to a double helix. b) The two strands of the duplex are represented in tube representations in dark and light gray, respectively. Two included DMSO molecules are shown in the CPK representation.

this short duplex and adopts a crescent-like conformation that apparently could be extended to a single helix without perturbing the duplex structure. Two molecules of DMSO are included in the duplex structure, with their oxygen atom hydrogen bonded to the amide protons of the 2,6-pyridinedicarboxamide units. However, ^{1}H NMR solution studies of **1** showed no evidence of stable duplex formation of guest binding in the helix hollow. In this respect, the behavior of **1** is consistent with that of Q^F_4 the aggregates of which could be characterized only at 243 K and high concentration (40 mM).[19]

The validity of the design principles of **2** were compellingly demonstrated by its crystal structure (Figure 2a). Its architecture is unprecedented in that it comprises a wide central $(Q^F_8)_2$ *double* helical subunit each strand of which spans two turns with a pitch of 7 Å, and two narrower peripheral Q_3P_3 *single* helical subunits each spanning another two turns with a pitch of 3.5 Å. As a consequence of the hybridization, the bulky *tert*-butyl groups do not lie at the ends of the structure despite their position at the end of the sequence. Instead, they are found at the border between single helical and double helical segments. However, no steric hindrance or perturbation of the helical shape results because the diameter of the single helical segments is reduced; this avoids clashes with the *tert*-butyl groups. The central antiparallel double helix of **2** is superimposable to that of the $(\text{Boc-}Q^F_8\text{-OMe})_2$ duplex that we previously characterized.[19] In particular, the relative position of the two strands, that is, the extent to which they are entwined into one another, is the same in the two duplexes. This perfect conservation of the $(\text{Boc-}Q^F_8\text{-OMe})_2$ duplex architectures is remarkable and was not obvious a priori considering the size of the Q_3P_3 extensions. Hybridization in this series appears to be dominated by the propensity of Q^F units to arrange pairwise in a head-to-tail fashion.

Studies were carried out to assess the extent of hybridization of **2** in solution. At low concentration, ^{1}H NMR spectra in $CDCl_3$ show one set of sharp lines. Upon increasing concentration (Figure 3) or lowering temperature (see the Supporting Information) a second set of signals emerges at

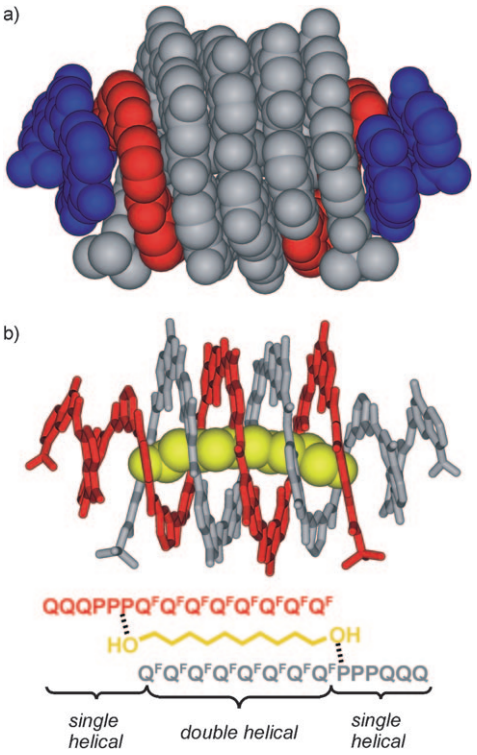


Figure 2. Structure of $HO(CH_2)_{10}OH\subset(\mathbf{2})_2$ in the solid state. Isobutyl side chains, the included solvent molecules, and hydrogen atoms have been omitted for clarity. a) The CPK view shows the monomers and is color coded as follows: Q in blue, P in red, Q^F in gray. The red and blue units belong to single helical segments, whereas the gray units belong to a double helix. b) The two strands of the capsule are represented in tube representations in red and gray, respectively. An encapsulated 1,10-decane-diol molecule is shown in yellow.

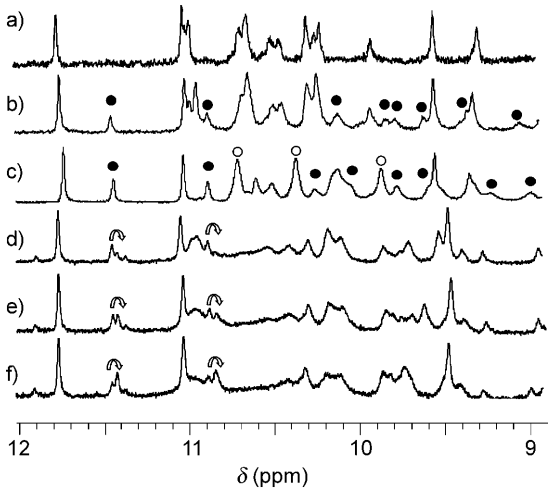


Figure 3. Part of the ^{1}H NMR spectra showing the amide resonances of **2** in $CDCl_3$ at 25 °C at: a) 0.2 mM; b) 1.0 mM; c) 5.0 mM; and titration of **2** in $CDCl_3$ (2 mM) at 25 °C with 1,10-decanediamine: d) 1.0 equiv; e) 2.5 equiv; f) 5.0 equiv. Peaks assigned to the double helical capsule (without guest) are shown as black circles. Peaks assigned to the single helix (without guest) are shown as white circles. Arrows indicate the conversion of the empty capsule into a capsule–guest complex.

higher field; this indicates stronger ring current effects. This pattern is consistent with a slow exchange on the NMR timescale between a single helical and a double helical form of **2**, as observed for other aromatic amide foldamers[18,19] and in particular for Boc-Q^F_8-OMe.[19] Based on the proportions between single and double helices, a dimerization constant $K_{dim} = 250\ L\,mol^{-1}$ can be calculated. This value is notably smaller—by more than three orders of magnitude—than that of Boc-Q^F_8-OMe, indicating that the large P_3Q_3 segment of **2** disfavors duplex formation.

Host–guest properties of 2: As explained above, the sequence of **2** was designed to bind to elongated diamine or diol guest molecules. This property was assessed both in the solid state and in solution. Two crystal structures of inclusion complexes of a guest within double helical **2** were obtained. The structure shown in Figure 2 is that of $HO(CH_2)_{10}OH\subset(\mathbf{2})_2$ and shows an excellent match between the cavity size and the guest length: the terminal hydroxyl groups lie in the same plane as (and form two hydrogen bonds with) the 2,6-pyridinedicarboxamide units. These hydrogen bonds presumably represent the main driving force of guest complexation. The structure of $HO(CH_2)_{10}OH\subset(\mathbf{2})_2$ shows the complete surrounding of the host around the guest, which is completely isolated from the solvent once encapsulated. This structure must undergo substantial conformational changes to capture and release a guest, such as 1,10-decanediol. A possible pathway could involve the partial unfolding of the terminal Q_3P_3 single helical segment, which would create an opening at the end of the cavity. Alternatively, guest binding could occur while the host exists as a single helix and hybridization takes place with the guest prelocated in the binding pocket.

The structure of $HO(CH_2)_9OH\subset(\mathbf{2})_2$ was also obtained. It is very similar to the above as far as the conformation of $(\mathbf{2})_2$ is concerned. However, it shows that the guest is slightly too short to simultaneously bind to the 2,6-pyridinedicarboxamide units at both its extremities. Instead, the guest has to slide in one direction or the other to form hydrogen bonds with the host, and disorder and partial occupancy factors are observed at the guest's terminal functions (Figure 4).

Binding studies in solution confirmed the solid-state observations, but were complicated by relatively weak binding constants, multiple exchange phenomena and extensive overlap of ^1H NMR signals belonging to different species. An NMR titration of **2** with 1,10-decanediamine (Figure 3) showed chemical-shift variations of the amide signals of the open ended single helix; this indicates binding in a fast-exchange regime. Broadening of these signals is also observed, which we have previously assigned to exchange between guest-amine and host-amide protons in other titrations with aliphatic amines of capsule $Q_3P_3Q^F_2A^FQ^F_2P_3Q_3$.[17a,21] The titration concomitantly revealed the emergence of a second set of signals very near to those of the empty duplex $(\mathbf{2})_2$; we attributed these to the host–guest complex observed in the solid state in slow exchange with empty $(\mathbf{2})_2$. A binding constant of the guest by the double helical capsule of the order of $200\ L\,mol^{-1}$ was estimated from the proportions of the two sets of signals. The saturation of both $(\mathbf{2})_2$ (disappearance of the signals of the empty guest) and of single helical **2** (chemical shifts reach a limit value) was almost complete after the addition of 10 equivalents of guest. Saturation resulted in a slight increase of the proportion of strands involved in double helices from 25 to 40% with respect to the single helical monomer. This small variation indicates that guest binding is stronger in the duplex than with the single helix, but not much stronger despite the additional hydrogen bonds that occur at both ends of the guest in the duplex. It should be pointed out that the duplex (Boc-Q^F_8-OMe)$_2$ alone, which constitutes the central section of $(\mathbf{2})_2$, does not show any affinity for alkane diols or diamines. Binding enthalpy can thus be assigned to hydrogen bonding between the pyridine–carboxamide moieties and the guest's polar functions.

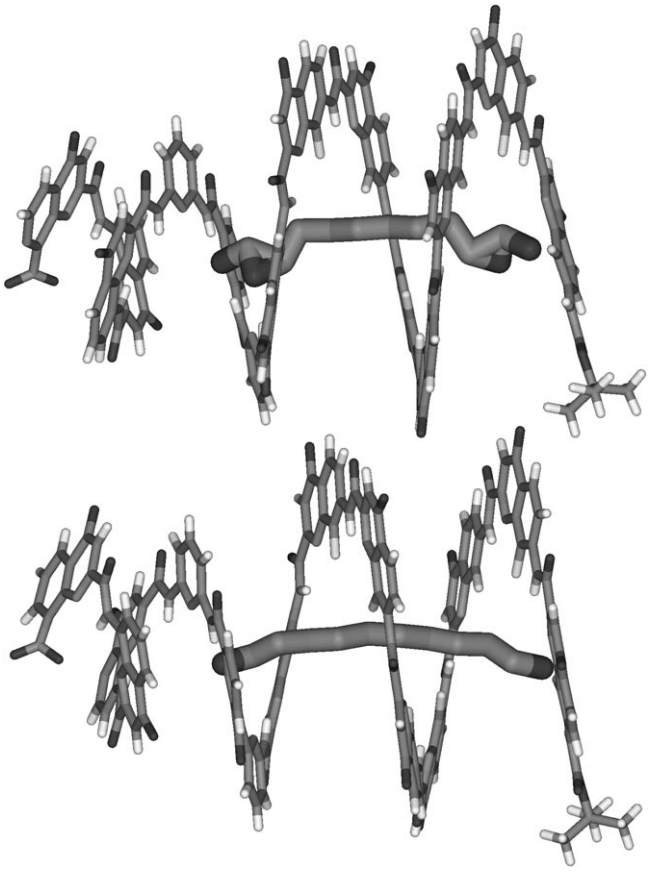


Figure 4. Structures of $HO(CH_2)_9OH\subset(\mathbf{2})_2$ (top) and $HO(CH_2)_{10}OH\subset(\mathbf{2})_2$ (bottom) in the solid state. Only one strand of the double helical capsule is shown, along with the entire guest molecule. Isobutyl side chains and included solvent molecules have been removed for clarity. The ends of the 1,9-nonanediol chains are disordered and the terminal atoms only have partial occupancy factors. The terminal hydroxyl groups nevertheless occupy identical positions in the two structures and are hydrogen bonded to the amide protons of the 2,6-pyridine dicarboxamide unit of **2**.

Titrations of **2** (2 mM) with 1,9-nonanediol, 1,10-decanediol and 1,11-undecanediol led to similar results (see the Supporting Information) and gave rise to a final proportion

of strands involved in double helices of 40, 70, and 30%, respectively. The stronger effect of decanediol with respect to nonanediol and undecanediol corroborates the better complementarity of decanediol with the host's cavity observed in the solid state. Finally, titration of **2** was also carried out with tBu-$CO_2(CH_2)_6NH_2$. Because it bears a bulky group, this guest was expected to bind to the single helical form of **2** and not to the duplex $(\mathbf{2})_2$. This prediction proved to be correct (see the Supporting Information) but binding was weak ($<80\ L\,mol^{-1}$) and did not result in a significant enhancement of the proportion of single helix.

Conclusions

For the purpose of designing synthetic capsules, self-assembly has the advantage of synthesis efficiency as it can be based on small and accessible building blocks. On the other hand, folding of oligomeric sequences provides access to complexity and tunability. We have shown here that these two approaches can be advantageously combined into one design. Double helical capsules, as the one described here, represent unprecedented objects in terms of their architecture but also in terms of the opportunities that they offer for guest binding and release, which might proceed through duplex dissociation or through the unfolding of a single helical cap at one end of a duplex. This work also demonstrates that monomers in a foldamer sequence can be simultaneously encoded with several distinct properties: helix diameter of the folded structure, recognition groups point towards the helix hollow and propensity to adopt single or double helical conformations. Aromatic amide foldamers thus offer a highly modular approach towards receptor design. Current efforts in our groups aim at further expanding the registry of available monomers and at improving synthesis methods to reach larger molecular containers with designed properties.

Experimental Section

General: All reactions were carried out under a dry nitrogen or argon atmosphere. Unless otherwise noted, the original materials were used directly from commercial suppliers without any purification. Dry THF was distilled from Na/benzephenone, dry dichloromethane and diisopropylethylamine (DIEA) were distilled from CaH_2 prior to use. NMR spectra were recorded by using a Bruker DMX 300 and Bruker AVANCE 400 spectrometers. Chemical shifts are expressed in parts per million (δ, ppm) using residual solvent protons as internal standards (chloroform $\delta=7.26$ ppm; DMSO $\delta=2.50$ ppm). Coupling constants are expressed in Hertz. EI, ESI mass spectra and MALDI-TOF were obtained by using GCT, LC-MS 2010, and Autoflex spectrometers, respectively.

Trimer 4: A solution of pivaloyl chloride (64 mg, 0.53 mmol) in CH_2Cl_2 (10 mL) was added via a syringe at 0°C to a solution of the trimer monoamine **3**[22] (200 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) containing DIEA (0.15 mL, 2.0 mmol). The reaction mixture was kept at 0°C for another 10 min and then at room temperature, overnight. The solution was evaporated and the crude was purified by flash chromatography (SiO_2) and eluted with MeOH/CH_2Cl_2 (3:97 v/v) to obtain an intermediate with both a Boc and a pivaloyl group as a white solid (191 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=9.87$ (s, 1H), 9.85 (s, 1H), 8.56 (d, J(H,H)=7.8, 2H), 8.23–8.06 (m, 4H), 7.98 (s, 1H), 7.87–7.78 (m, 3H), 7.09 (s, 1H), 1.55 (s, 9H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=176.9$, 161.4, 152.1, 150.5, 150.1, 148.9, 148.8, 148.6, 141.1, 140.9, 139.6, 125.9, 102.3, 109.9, 108.7, 81.3, 39.9, 28.3, 27.5. MS (ESI): m/z 534.2 $[M+H]^+$. This compound (170 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (10 mL) and excess TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4 and then concentrated to give trimer **4** as a light yellow solid. This compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=10.07$ (s, 1H), 9.96 (s, 1H), 8.54 (d, J(H,H)=7.8, 2H), 8.19 (m, 2H), 8.04 (d, J(H,H)=8.1, 2H), 7.86–7.80 (m, 2H), 7.60 (t, J(H,H)=7.8, 1H), 6.38 (d, J(H,H)=7.8, 1H), 4.54 (s, 2H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=177.0$, 161.3, 161.1, 157.3, 150.1, 149.0, 148.9, 148.6, 148.3, 141.1, 140.5, 139.6, 125.8, 125.7, 110.2, 109.7, 105.1, 103.6, 39.9, 37.3. MS (ESI): m/z 434.4 $[M+H]^+$.

Pentamer 6: Trimer **4** (68 mg, 0.16 mmol) and DIEA (0.1 mL, 1.27 mmol) were dissolved in dry CH_2Cl_2 (10 mL); the freshly prepared dimer acid chloride **5**[19] (110 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was added dropwise at room temperature. The solution was stirred, overnight, was then evaporated and the product was purified by flash chromatography (SiO_2) and eluted with cyclohexane/EtOAc (7:3 v/v) to obtain pentamer **6** as a white solid (135 mg, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=10.82$ (s, 1H), 10.76 (s, 1H), 10.17 (s, 1H), 10.16 (s, 1H), 8.87 (t, J(H,H)=7.2, 1H), 8.56–8.52 (m, 2H), 8.46 (t, J(H,H)=7.2, 1H), 8.20–8.16 (m, 3H), 8.10 (d, J(H, H)=7.8, 1H), 8.05 (m, 1H), 8.00 (d, J(H,H)=7.8, 2H), 7.90 (t, J(H,H)=8.1, 1H), 7.75 (d, J(H,H)=8.1, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.49 (t, J(H,H)=7.8, 1H), 7.19 (s, 1H), 4.12 (t, J(H,H)=6.3, 4H), 2.32–2.30 (m, 2H), 1.66 (s, 9H), 1.21–1.17 (m, 12H), 0.97 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=176.9$, 163.1, 162.3, 162.1, 161.6, 161.2, 152.3, 151.0, 150.6, 150.1, 149.5, 149.3, 148.9, 140.6, 140.0, 139.2, 127.5, 127.4, 127.2, 127.0, 125.9, 120.2, 119.4, 118.5, 117.5, 117.1, 110.4, 110.3, 110.2, 109.9, 109.8, 109.7, 97.9, 97.6, 81.4, 75.4, 75.3, 39.4, 28.3, 28.1, 26.9, 19.2. MS (ESI): m/z 1054.5 $[M+H]^+$.

Heptamer 8: Pentamer **6** (120 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4 and then concentrated to give pentamer amine **7** as a light yellow solid, which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=10.96$ (s, 1H), 10.75 (s, 1H), 10.03 (s, 2H), 8.89 (t, J(H,H)=7.5, 1H), 8.57–8.54 (m, 2H), 8.25–8.11 (m, 5H), 7.97–7.88 (m, 3H), 7.82 (d, J(H,H)=8.1, 1H), 7.75 (s, 1H), 7.62–7.55 (m, 2H), 7.11 (t, J(H,H)=8.1, 1H), 4.22 (s, 2H), 4.15 (d, J(H,H)=6.6, 2H), 4.10 (d, J-(H,H)=6.6, 2H), 2.37–2.27 (m, 2H), 1.20–1.15 (m, 12H), 1.00 (s, 9H). MS (ESI): m/z 954.5 $[M+H]^+$. The freshly prepared dimer acid chloride **5**[19] (77.6 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of amine **7** (100 mg, 0.10 mmol) and DIEA (0.1 mL, 0.6 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred, overnight, solvents were evaporated and the product was purified by flash chromatography (SiO_2) and eluted with cyclohexane/EtOAc (3:1 v/v) to obtain heptamer **8** as a white solid (85 mg, 52%). ^{1}H NMR ([D_5]DMSO, 300 MHz): $\delta=11.47$ (s, 1H), 11.28 (s, 1H), 11.02 (s, 1H), 10.42 (s, 1H), 10.08 (s, 1H), 9.94 (s, 1H), 9.20 (s, 1H), 8.48 (t, J(H,H)=8.1, 1H), 8.06 (d, J-(H,H)=6.6, 1H), 7.94 (t, J(H,H)=8.1, 2H), 7.86–7.82 (m, 3H), 7.70 (d, J(H,H)=7.5, 2H), 7.63–7.56 (m, 4H), 7.23 (d, J(H,H)=9.0, 1H), 7.16–7.14 (m, 2H), 6.96–6.94 (m, 3H), 6.83 (t, J(H,H)=8.1, 1H), 6.67 (d, J-(H,H)=8.4, 1H), 6.52 (s, 1H), 4.34–4.17 (m, 6H), 4.08–4.00 (m, 2H), 2.42–2.27 (m, 4H), 1.35–1.20 (m, 33H), 0.67 (s, 9H). MS (ESI): m/z 1574.54 $[2M+2H]^{2+}$, 1586.54 $[2M+Na+H]^{2+}$, 1596.51 $[2M+2Na]^{2+}$.

Heptamer amine 1: Heptamer **8** (80 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (10 mL) and excess TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4 and then concentrated to give heptamer amine **1** as a light yellow solid. ^{1}H NMR ([D_5]DMSO, 300 MHz): $\delta=$ 11.49 (s, 1H), 11.24 (s, 1H), 10.79 (s, 1H), 10.29 (s, 1H), 10.18 (s, 1H),

10.05 (s, 1H), 9.02 (s, 1H), 8.55 (t, J(H,H) = 8.1, 1H), 8.30–8.26 (m, 1H), 8.10 (d, J(H,H) = 7.5, 1H), 7.97 (t, J(H,H) = 7.5, 1H), 7.73 (t, J(H,H) = 7.5, 2H), 7.66 (d, J(H,H) = 7.2, 1H), 7.50–7.27 (m, 8H), 6.90 (t, J(H,H) = 8.7, 2H), 6.75 (t, J(H,H) = 8.1, 2H), 6.57 (t, J(H,H) = 8.1, 1H), 6.46 (d, J(H,H) = 7.5, 1H), 4.36 (s, 2H), 4.29–4.28 (m, 2H), 4.19–4.10 (m, 4H), 3.96–3.95 (m, 2H), 2.40–2.27 (m, 4H), 1.27–1.18 (m, 24H), 0.65 (s, 9H). MS (ESI): m/z 1474.54 $[2M+2H]^{2+}$, 1486.54 $[2M+Na+H]^{2+}$.

Decamer 10: A solution of acid chloride **5**[19] (70 mg, 0.1 mmol) in THF (10 mL) was added via a syringe to a solution of octamer amine **9**[17a] (170 mg, 0.10 mmol) in THF (20 mL) containing DIEA (0.04 mL, 0.5 mmol). The reaction mixture was stirred at room temperature, overnight. The solution was evaporated and the crude was purified by flash chromatography (SiO_2) and eluted with cyclohexane/EtOAc (50:50 v/v) to obtain decamer **10** as a light yellow solid (140 mg, 63% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.90 (s, 1H), 11.33 (s, 1H), 10.90 (s, 1H), 10.78 (s, 1H), 10.72 (s, 1H), 10.37 (s, 1H), 10.11 (s, 1H), 9.84 (s, 1H), 9.25 (s, 1H), 9.04 (t, J(H,H) = 7.8, 1H), 8.80 (d, J(H,H) = 7.2, 2H), 8.29 (d, J(H,H) = 7.2, 2H), 8.21 (d, J(H,H) = 7.8, 2H), 8.15–8.11 (m, 3H), 7.93–7.82 (m, 6H), 7.64 (d, J(H,H) = 7.8, 2H), 7.58–7.54 (m, 2H), 7.50–7.48 (m, 2H), 7.38–7.34 (m, 4H), 7.21 (d, J(H,H) = 7.8, 1H), 6.97 (t, J(H,H) = 7.8, 1H), 6.85–6.73 (m, 2H), 6.73 (s, 1H), 6.44 (s, 1H), 6.33 (t, J(H,H) = 7.8, 1H), 4.25–4.10 (m, 9H), 3.87 (d, J(H,H) = 7.2, 1H), 3.71 (d, J(H,H) = 4.8, 3H), 3.65 (d, J(H,H) = 7.2, 1H), 2.42–2.40 (m, 4H), 2.13–2.06 (m, 3H), 1.86 (s, 9H), 1.39–1.23 (m, 32H), 1.11–0.99 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 163.8, 163.1, 162.9, 162.8, 162.7, 162.2, 162.2, 161.9, 161.6, 161.3, 161.1, 160.8, 154.2, 152.2, 151.2, 150.9, 150.6, 150.5, 150.4, 149.4, 149.2, 148.9, 148.8, 148.2, 148.1, 145.2, 145.1, 140.4, 139.4, 139.3, 139.0, 138.9, 138.5, 137.4, 134.9, 134.4, 128.3, 127.2, 127.1, 126.8, 126.7, 126.5, 125.9, 125.5, 124.7, 124.5, 123.7, 122.3, 121.6, 120.4, 120.3, 119.8, 119.7, 119.6, 118.7, 118.4, 118.2, 118.0, 117.8, 117.6, 117.2, 116.6, 116.2, 116.0, 111.3, 109.4, 108.9, 108.6, 99.5, 99.1, 98.2, 98.1, 97.9, 97.5, 81.3, 75.8, 75.7, 75.6, 75.5, 75.2, 75.0, 28.7, 28.6, 28.4, 28.3, 19.9, 19.8, 19.7, 19.6, 18.5, 18.4. MS (ESI): m/z 2248.0 $[2M+2H]^{2+}$, 2259.0 $[2M+H+Na]^{2+}$, 2270.0 $[2M+2Na]^{2+}$.

Capsule 2: Decamer **10** (120 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (10 mL) and excess TFA (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4 and then concentrated to give decamer amine **11** as a yellow solid, which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.85 (s, 1H), 11.29 (s, 1H), 10.84 (s, 1H), 10.74 (s, 1H), 10.65 (s, 1H), 10.34 (s, 1H), 10.21 (s, 1H), 9.77 (s, 1H), 9.36 (s, 1H), 8.92. (t, J(H,H) = 7.2, 1H), 8.76 (d, J(H,H) = 7.5, 2H), 8.25 (d, J(H,H) = 7.8, 1H), 8.11–7.64 (m, 4H), 7.88–7.79 (m, 4H), 7.61 (d, J(H,H) = 7.2, 1H), 7.55 (d, J(H,H) = 7.5, 2H), 7.47 (d, J(H,H) = 7.5, 1H), 7.38–7.31 (m, 6H), 7.21–7.12 (m, 4H), 6.89 (t, J(H,H) = 7.8, 1H), 6.83 (s, 1H), 6.75 (d, J(H,H) = 7.2, 1H), 6.65–6.54 (m, 2H), 6.33(t, J(H,H) = 7.8, 1H), 4.26–4.03 (m, 9H), 3.83–3.78 (m, 1H), 3.70–3.58 (m, 4H), 3.27 (s, 2H), 2.47–2.29 (m, 4H), 2.15–2.04 (m, 3H), 1.35–1.22 (m, 32H), 1.16–0.96 (m, 10H); MS (ESI): m/z 1074.5 $[M+2H]^{2+}$. A solution of acid chloride **12**[19] (50 mg, 0.05 mmol) in THF (10 mL) was added dropwise through a syringe to a solution of decamer amine **11** (80 mg, 0.04 mmol) in THF (10 mL) containing DIEA (0.02 mL, 0.27 mmol). The reaction mixture was stirred at room temperature, overnight. The solution was evaporated and the product was purified by flash chromatography (SiO_2) and eluted with cyclohexane/EtOAc (50:50 v/v) to give **2** (30 mg, 25% yield) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.74 (s, 1H), 10.99 (s, 1H), 10.91 (s, 1H), 10.66 (s, 1H), 10.62 (s, 1H), 10.46 (s, 1H), 10.41 (s, 1H), 10.27 (s, 1H), 10.20 (s, 1H), 10.11 (s, 1H), 9.89 (s, 1H), 9.52 (s, 1H), 9.27 (s, 1H), 8.94–8.76 (m, 3H), 8.67–8.57 (m, 2H), 8.32–8.12 (m, 5H), 8.02 (d, J(H,H) = 8.1, 1H), 7.98 (d, J(H,H) = 7.8, 2H), 7.93–7.86 (m, 2H), 7.82–7.68 (m, 5H), 7.63–7.59 (m, 2H), 7.54–7.32 (m, 12H), 7.17–7.07 (m, 6H), 6.94 (d, J(H,H) = 5.1, 1H), 6.77 (s, 1H), 6.67 (s, 1H), 6.57 (t, J(H,H) = 7.5, 1H), 6.44 (s, 2H), 4.40–3.95 (m, 16H), 3.75–3.51 (m, 6H), 2.55–2.24 (m, 11H), 1.61 (s, 9H), 1.43–1.21 (m, 66H); MS (ESI): m/z 1644.4 $[M+2H]^{2+}$, 1655.4 $[M+H+Na]^{2+}$.

X-ray crystallography: Suitable crystals for diffraction experiments of compound $(\mathbf{1})_2$ were grown from a supersaturated DMSO solution. Data were collected by using a Rigaku rapid diffractometer equipped with an MM007 microfocus rotating anode generator with monochromatized $Cu_{K\alpha}$ radiation (1.54178 Å), varimax optics and a RAPID image plate. Suitable crystals for diffraction experiments of compounds $HO(CH_2)_9OH\subset(\mathbf{2})_2$ and $HO(CH_2)_{10}OH\subset(\mathbf{2})_2$ were grown by liquid–liquid diffusion techniques from chloroform/methanol mixtures. The nicely shaped crystals of 0.008 mm^3 in size were not diffracting enough on our home source to solve the structure by using ab initio methods. Data were thus collected at the ESRF synchrotron in Grenoble on the ID29 beamline. The wavelength was set to 0.8265 Å and all data were collected at 100 K. During data collection severe radiation damage was observed that could explain the poor final crystallographic statistics. Software used: XDS (data reduction),[23] SHELXD (structure solution),[24] SHELXL-97 (structure refinement),[24] Win GX (crystallographic data preparation).[25] All C-bonded H atoms were placed at calculated positions and refined by using a riding model, with C–H distances of 0.93–0.96 Å. The N- and O-bonded H atoms were refined with free positional parameters. The H-atom Uiso parameters were fixed at 1.2 eq(N) for the N–H group, at 1.2 Ueq(O) for the O–H group, at 1.2 Ueq(C) for methine and methylene C–H and at 1.5 Ueq(C) for methyl C–H.

Crystals of $(\mathbf{1})_2$ belong to the triclinic $P\bar{1}$ space group with unit cell parameters a = 20.127, b = 20.135, c = 25.661 Å; α = 89.98, β = 89.99, γ = 60.72°. We should note that both α and β angles were close to 90° but due to disordered solvent molecules it was not possible to solve the structure in a higher symmetry space group. Other crystallographic and data collection parameters are: M_r = 3506.77, V = 9070.69(11) Å^3, Z = 4, μ = 1.250 mm^{-1}, no absorption correction, omega scans, 32385 reflections collected, θ_{max} = 72.51°, 9052 independent (R_{int} = 0.099), $[I \geq 2\sigma[(I)]$, R = 0.1074, $wR2$ = 0.3046.

$HO(CH_2)_9OH\subset(\mathbf{2})_2$ crystals belong to the monoclinic $C2/c$ space group with unit cell parameters a = 32.963, b = 40.911, c = 38.539 Å; β = 98.16°. Other crystallographic and data collection parameters are: M_r = 3479.78, V = 51446(18) Å^3, ρ_{calcd} = 0.904 g cm^{-3}, Z = 8, μ = 0.088 mm^{-1}, no absorption correction, ϕ scans, 53432 reflections collected, θ_{max} = 25.51°, 26660 independent (R_{int} = 0.068), $[I \geq 2\sigma(I)]$, R = 0.1571, $wR2$ = 0.3921.

$HO(CH_2)_{10}OH\subset(\mathbf{2})_2$ crystals belong to the monoclinic $C2/c$ space group with unit cell parameters a = 34.398, b = 40.263, c = 38.827 Å; β = 98.86°. Other crystallographic and data collection parameters are: M_r = 3424.21, V = 53132(18) Å^3, ρ_{calcd} = 0.811 g cm^{-3}, Z = 8, μ = 0.062 mm^{-1}, no absorption correction, ϕ scans, 56265 reflections collected, θ_{max} = 29.27, 22806 independent (R_{int} = 0.076), $[I \geq 2\sigma(I)]$, R = 0.1865, $wR2$ = 0.4358.

CCDC-725946 (**1**), 20253 ($HO(CH_2)_9OH\subset(\mathbf{1})_2$) and 20252 ($HO(CH_2)_9OH\subset(\mathbf{2})_2$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

This work was supported by a French ANR grant (project no. NT05-3_44880), the Chinese Academy of Sciences "Hundred Talents Program", the National Natural Science Foundation of China (20772127) and the National Basic Research 973 Program of China (grant no. 2009CB930802). We thank Dr. Christoph Mueller-Dieckmann at ESRF for his help during data collections on ID29 Beamline.

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Received: April 2, 2009
Published online: September 18, 2009

