Molecular Recognition

Molecular Apple Peels**

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Molecular encapsulation, defined here as the complete isolation of guest molecules from the solvent within a molecular or supramolecular container, has attracted widespread interest because of the applications it may have, for example, in molecular recognition and catalysis,[1] and because of the new insights it gives on otherwise unstable guest species that are protected from degradation within a secluded environment.[2] Several strategies are available to create a closed shell around a cavity. On the one hand, capsules may be unimolecular and consist of polymacrocyclic structures[1a,3] or of deep bowl-shaped molecules with a bulky rim,[4] while on the other hand, capsules may be formed by self-assembly of several molecular components. Examples of this latter category illustrate the numerous possibilities for

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dividing the surface of a sphere[1d,e] (for example, two hemispherical halves,[5] two non-hemispherical sections,[6] four quarters,[7]) or of a polyhedron[1b,c] (for example, tetrahedron,[8] icosahedron,[9] snub cube,[10] triangular prism[11]) into complementary elements. Herein we present a new approach for preparing unimolecular capsules from a molecular strand folded into a helix, the diameter of which is large at the center and reduced at both ends—similar to the shape of the skin of an apple peeled in a helical fashion.[12]

Some helices possess a hollow large enough to channel ions through biological membranes[13] or to host organic guest molecules.[14–18] Helices derived from aromatic oligoamides (AOAs) may prove particularly suitable for the purpose of molecular recognition because their diameter can be tuned at will according to the size of the monomers and the orientation of the amine and acid groups on each aromatic ring.[16–21] Thus, hollows as large as 3 nm[19] and as low as 0.5 nm[17,18] have been reported for AOAs. A refinement of this concept is the design of an oligomeric sequence comprising both monomers that code for helical segments with a hollow and monomers that code for no hollow at all. If the former are introduced at the center of the sequence and the latter are located at both ends, a helix defining a closed shell—a helix with both its extremities capped—may result and allow the encapsulation of guest species (Figure 1). The mechanism of binding a guest

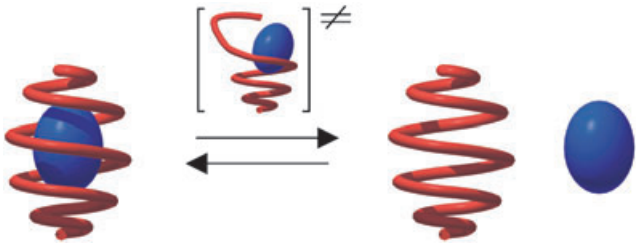
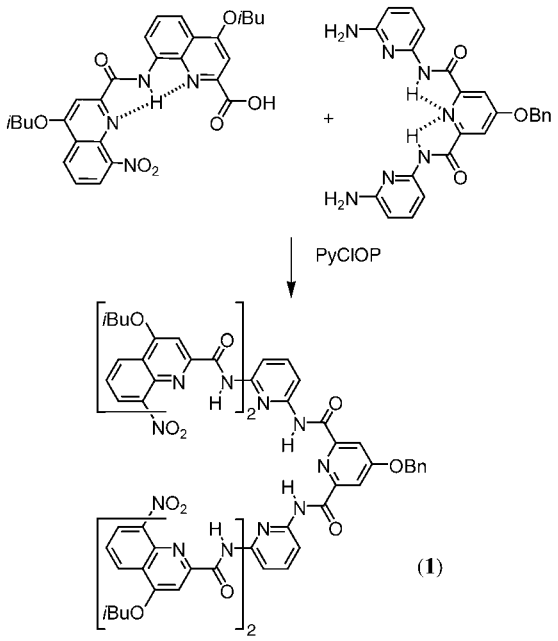


Figure 1. Encapsulation of an egg-shaped guest by partial unfolding of a helix possessing a reduced diameter at both ends.

in a capsule of this kind is expected to differ from the simple binding of a guest in the open hollow of a helix because it requires a partial unfolding of the capsule (Figure 1).[1e] This design also represents a novel way to relate the secondary structure and the chemical function of an oligomer to the primary sequence of its monomers.

To validate this concept we designed the prototypical capsule **1** (Scheme 1) which should be able to accommodate a small but highly relevant guest such as water. The hollow defined by helices of oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid is highly polar and can bind water in the solid state[18] and in solution.[17] However, oligoamides of 8-amino-2-quinolinecarboxylic acid form very stable helices with a hollow too small to accommodate any guest.[21] Oligomer **1** combines a central trimeric segment of pyridine monomers flanked by two short dimeric segments of quinoline monomers. Preliminary modeling studies showed that the central unit should form a sort of bulge large enough to bind a water molecule whilst the peripheral units should cap the helix hollow and possibly trap the guest.



Scheme 1. Structure and synthesis of oligomer **1**. The dashed lines indicate hydrogen bonds that contribute to the stabilization of the helical conformation of **1**. Bn = benzyl, py = pyridyl.

The oligomer was prepared in one step from the previously described central trimeric unit[18a] and peripheral dimeric units[21] (Scheme 1). Evidence that oligomer **1**[22] can indeed encapsulate a small guest came from X-ray diffraction analysis of a single crystal grown from the slow diffusion of heptane into a toluene solution (Figure 2).[23] The solid-state structure reveals the expected helical shape that spans over two full turns. The pitch equals the thickness of one aromatic ring (about 3.45 Å), as found in previous structures of pyridine and quinoline oligomers.[17,18,21] The CPK views show that the terminal quinoline units do cap the hollow defined by the pyridine segment—the inner diameter of the helix is reduced at both ends. Most importantly, the helices all contain one molecule of water despite the low water content of the unpolar crystallization medium. The water oxygen atom is hydrogen bonded to the two amide protons of the central pyridine-2,6-dicarboxamide units (d_{N-O}: 2.84 Å, N-H-O: 150.1°) and sandwiched between the terminal nitro groups. The water molecule is completely surrounded by the helix and not visible from the outside. This observation implies that the binding and release of the water molecule in solution involves a partial unfolding or a springlike extension of the strand[24] (Figure 1). The kinetics of such a process should fundamentally differ from the binding and release of a guest from the open hollow of a normal cylindrical helix.[1e]

The behavior of **1** in solution was studied by NMR spectroscopy to test this hypothesis. The ^{1}H NMR spectrum of **1** in $CDCl_3$ possesses all the characteristic features of folded helices formed from oligomers with only pyridine[17,18] or only quinoline[21] units: sharp lines, spreading of the signals over a wide range of chemical shifts, downfield shifts of the signals of the amide protons involved in intramolecular hydrogen bonding, shielding of the protons involved in intramolecular

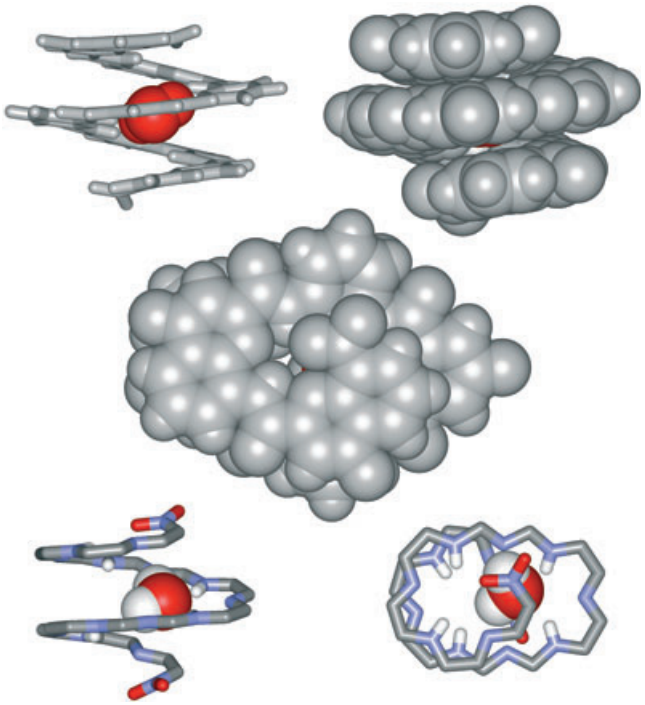


Figure 2. Views of the structure of $H_2O\subset$**1** in the crystal. Isobutyl and benzyl chains as well as included toluene molecules have been omitted for clarity. The hydrogen atoms of the water molecule could not be located and their positions are hypothesized from X-ray structures in which they could be determined.[18] The CPK views clearly show that the water is completely isolated from the surrounding medium. The two bottom structures only show the inner rim of the capsule and its numerous polar functions converging towards the hollow.

π–π stacking (Figures 3 and 4). No diastereotopic patterns of the signals of the methylene protons of the side chains are observed at room temperature, thus indicating that the equilibrium between the right-handed and the left-handed helices is fast on the NMR timescale, and that partial unfolding of the helix does occur. Of note is that the chemical shift of the amide protons appears to be dependent on their positions in the sequence. Whilst the most peripheral amide protons give rise to signals at $\delta = 11.62$ and 10.08 ppm, the amide protons of the central pyridinedicarboxamide monomer are strongly shielded and their signal appears at $\delta =$ 8.62 ppm (Figure 3a). Aromatic stacking is probably responsible for this upfield shift. Indeed, the crystal structure of **1** shows that these amide protons are sandwiched between the two terminal quinoline rings in the helix and should be strongly exposed to ring-current effects (Figure 2).

A first indication that water is bound in the helix hollow not only in the solid state but also in solution came from the variation of the chemical shifts of the NH protons with the water content of the chloroform. Samples were prepared using $CDCl_3$ dried over activated alumina and $CDCl_3$ saturated with H_2O. Drying or wetting the solvent had little effect on the chemical shift of the two signals of the four peripheral amide protons ($\Delta\delta < 0.2$ ppm). However, large variations in the position of the signal of the most central amide protons were observed: this signal shifted upfield to $\delta = 8.08$ ppm upon drying[25] (Figure 3d) but shifted downfield to $\delta = 9.39$ ppm upon wetting the solvent[26] (Figure 3c). This variation of cgemical shift ($\Delta\delta = 1.31$ ppm) is consistent with the hydrogen bonding of these amide protons to the oxygen atom of a water molecule, as seen in the solid state.

Additionally, the three amide protons undergo very different rates of exchange with deuterons in the presence of an excess of D_2O.[26] The amide protons of the central unit protrude into the helix cavity and hydrogen bond to water, and are fully exchanged within 3 h. For comparison, the second amide protons from the center of the sequence are only partially exchanged after 24 h (< 87 %), and the most peripheral amides show no sign of exchange after 4 days.

When a sample of **1** in $CDCl_3$ "from the bottle"—that is not specially dried—is cooled down, the signal of the central amide protons progressively shifts downfield (to $\delta = 9.73$ ppm at −40 °C), similar to the situation when excess water is added to the solution at room temperature (Figure 3b). The binding of water is apparently favored upon cooling. Cooling also causes a broadening of the signal of residual water in the solvent which then separates into two signals at $\delta = 4.44$ ppm and $\delta = 1.81$ ppm (Figure 4). The signal at higher field is intense when the sample is wet and shifts downfield as the temperature decreases, thus suggesting that it corresponds to

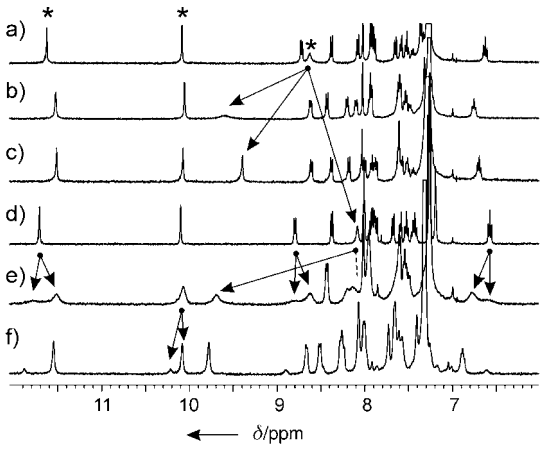


Figure 3. Part of the 400 MHz ^{1}H NMR spectra of **1** showing the amide and aromatic resonances: a) in $CDCl_3$ at 25 °C; b) in $CDCl_3$ at −20 °C; c) in "wet"[26] $CDCl_3$ at 25 °C; d) in "dried"[25] $CDCl_3$ at 25 °C, e) in "dried"[25] $CDCl_3$ at −20 °C; f) in "dried"[25] $CDCl_3$ at −50 °C. The asterisks indicate the resonances of the amide protons. The arrows indicate some corresponding signals.

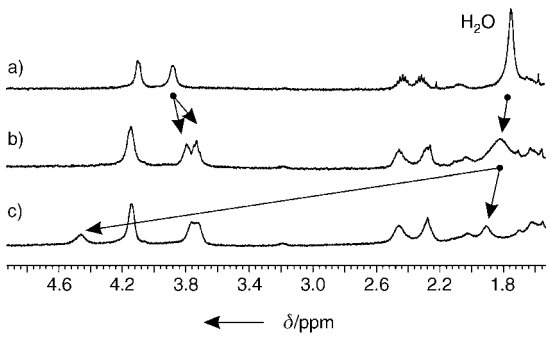


Figure 4. Part of the 400 MHz ^{1}H NMR spectra of **1** in $CDCl_3$ showing alkyl and water resonances: a) at 25 °C; b) at −30 °C; c) at −55 °C. The arrows link corresponding signals.

free water. The signal at lower field has an integration corresponding to two protons and its position changes very little with temperature. These signals are not seen when the solution is washed with D_2O. A NOESY spectrum recorded at −55 °C shows strong correlations corresponding to exchange phenomena and/or NOE interactions between the central amide NH protons which point towards the capsule cavity and the two signals of water at $\delta = 4.44$ and $\delta = 1.81$ ppm (see the Supporting Information). However, the two other types of amide protons show no such correlations. All these data are consistent with the assignment of the signal at $\delta = 4.44$ ppm to a molecule of water bound inside the helix cavity. Such a water molecule would be surrounded by polar amide groups, nitro groups, and endocyclic pyridine and quinoline nitrogen atoms which would result in a downfield shift of the signal of the bound water protons. As an indication of the polarity of the environment in the capsule, the chemical shift of $H_2O \subset \mathbf{1}$ is similar to the chemical shift of H_2O in D_2O. The binding constant of water by the capsule at room temperature is estimated to be of the order of 150 $L\,mol^{-1}$ from the chemical shift variations of the NMR signals of the amide protons and integration of the water signal.

Slow exchange of the water molecule on the NMR timescale is consistent with the diastereotopic pattern observed at low temperature for the signal of the CH_2 group of one isobutyl sidechain (signals at $\delta = 3.8$ ppm in Figure 4). The equilibrium between the right-handed and the left-handed helices, and thus the opening of the capsule, is slowed down. Such a slow exchange of the water molecule at low temperature is in sharp contrast with the behavior of oligoamides of diaminopyridine and pyridinedicarboxylic acid described previously and which do not bear quinoline end caps.[17] These helical oligomers were also shown to bind water in solution in their hollow,[17,18] but the exchange of water remains fast on the NMR timescale, even at temperatures as low as −55 °C. The quinoline end caps in oligomer **1** seem to be critical in slowing down the binding and release of the water molecule.

We were intrigued by the fact that bound water and free water are in slow exchange on the NMR timescale at low temperature, whereas no splitting of the signals of the capsule occurred; thus the filled capsule appears to be in fast exchange with the empty capsule. We attribute this discrepancy to the presence of a large excess of water in these experiments, which causes the saturation of the capsule at low temperature: most capsules are occupied and the small portion of empty capsules are rapidly filled because of the large excess of water. We thus measured the NMR spectra after having eliminated as much water as possible.[25] Upon cooling the solution we observed a broadening of the amide and of several aromatic signals of the capsule which split into two sets of signals having identical chemical shifts to those of the empty capsule, and to those of the full capsule, respectively (Figure 3 d–f). The signals of the empty and full capsule can thus be distinguished at low water content, although the full capsule remains the major species.

The aim of this study was to illustrate a new concept for creating molecular closed shells around a cavity that can bind to molecular guests. Ongoing research includes the preparation of more stable capsules that would release guests at even lower rates, and of larger capsules that could accommodate larger guests or more than one guest.

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[22] Physical data for **1**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, solvent as internal reference): $\delta = 11.62$ (s, 2H), 10.08 (s, 2H), 8.72 (d, $^3J(H,H) = 7.4$ Hz, 2H), 8.62 (s, 2H), 8.38 (d, $^3J(H,H) = 7.4$ Hz, 2H), 8.08 (d, $^3J(H,H) = 7.7$ Hz, 2H), 8.02 (s, 2H), 7.94–7.87 (m, 6H), 7.65 (d, $^3J(H,H) = 7.3$ Hz, 2H), 7.58 (d, $^3J(H,H) = 7.3$ Hz, 2H), 7.52 (t, $^3J(H,H) = 7.7$ Hz, 2H), 7.35–7.25 (m, 7H), 6.62 (t, $^3J(H,H) = 7.7$ Hz, 2H), 5.43 (s, 2H), 4.06 (d, $^3J(H,H) = 5.3$ Hz, 4H), 3.84 (s, 4H), 2.39–2.36 (m, 4H), 1.27 (d, $^3J(H,H) = 6.8$ Hz, 12H), 1.17 ppm (d, $^3J(H,H) = 6.8$ Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 162.32$, 161.94,161.36, 160.40, 153.03, 149.52, 148.84, 148.60, 148.49, 144.19, 140.16, 139.72, 137.17, 133.06, 128.64, 128.55, 127.58, 127.48, 127.01, 126.12, 123.49, 123.11, 121.02, 117.61, 116.23, 111.49, 110.26, 109.19, 98.99, 98.81, 74.87, 74.73, 70.58, 29.35, 29.01, 27.98, 27.69, 19.10, 18.97 ppm; IR (KBr): $\tilde{\nu} = 3155$, 2965, 2254, 1794, 1527, 1471, 1383, 1262, 1096, 1013, 908 cm^{-1}; TOF-MS: *m/z:* 1484.44 $[M+H]^+$, 1506.44 $[M+Na]^+$, 1522.44 $[M+K]^+$.

[23] Crystal data: **1:** $C_{80}H_{73}N_{15}O_{15}(C_7H_8)_{1.5}(H_2O)$, $M_r = 1640.75$, crystal size $0.15 \times 0.10 \times 0.10$, monoclinic, space group $P\bar{1}$, $Z = 2$, $a = 16.9588(12)$, $b = 17.2292(10)$, $c = 17.5449(10)$ Å, $\alpha = 114.178(1)$, $\beta = 92.719(1)$, $\gamma = 116.029(1)$°, $V = 4037.7(4)$ Å^3, $\rho_{calcd} = 1.350$ mg m^{-3}, $T = 193(2)$ K, $\theta_{min} = 2.87$, $\theta_{max} = 68.31$, $\lambda = 1.54180$ Å; $Cu_{K\alpha}$, $\mu(Cu_{K\alpha}) = 0.775$ mm^{-1}. Data collected on a Rigaku MM007-Rapid R-AXIS diffractometer. Of 71512 reflections measured, 14143 were unique ($R_{int} = 0.0851$), 8827 with $I > 2\sigma(I)$, 1093 parameters in final refinement. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (SHEXLTL version 6.12). The final R indices were R_1 ($I > 2\sigma(I)$) = 0.0738, $wR_2(F^2) = 0.2165$ (all data). CCDC 258147 contains 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.

[24] The springlike extension of related oligomers has been characterized in solution upon the formation of double-helical dimers; for a recent report see: H. Jiang, V. Maurizot, I. Huc, *Tetrahedron* **2004**, *60*, 10029 – 10038.

[25] Oligomer **1** was dissolved in dry toluene and water was removed azeotropically by distillation before evaporation under vacuum. $CDCl_3$ was filtered through activated alumina just before sample preparation.

[26] One drop added to 500 μL of $CDCl_3$.

