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Encapsulation of Small Polar Guests in Molecular Apple Peels

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Abstract: Three aromatic oligoamides have been prepared that have alternating 1,6-diaminopyridine and 1,6-pyridinedicarboxylic acid units at the center of the sequence and two 8-amino-2-quinolinecarboxylic acid units at each extremity. The three oligomers differ in the number--3, 5, or 7—of pyridine units in the sequence. They were designed to adopt helically folded conformations in solution and in the solid state. The sequence of monomers was chosen so that the diameter of the helix is larger in the center than at each extremity, and hence they resemble helically wrapped apple peels. According to modeling studies, the pyridine units were expected to define a polar hollow within the helix that is large enough to accommodate small polar guests, whereas the quinoline units at each end of the oligomeric sequences were expected to completely cap the hollow and transform the helix cavities into a closed shell that may act as a capsule. Crystallographic studies demonstrate that the oligomers do fold into helices that define a cavity isolated from the surrounding medium in the solid state. Depending on the number of pyridine rings, one or two water molecules are bound within the capsules. The crystal structure of a capsule fragment shows that MeOH can also be hosted by the largest oligomer. Solution NMR studies confirm that binding of water also occurs in solution with the same stoichiometry as observed in the solid state. The capsules have distinct signals depending on whether they are empty, half-full, or full, and these species are in slow exchange on the NMR timescale at low temperature. Indeed, the binding and release of water molecules requires a significant conformational distortion of the helix that slows down these processes. The addition of small polar molecules such as methanol, hydrazine, hydrogen peroxide, or formic acid to the largest capsule leads to the observation of new sets of NMR signals of the capsules that were assigned to complexes with these guests. However, water appears to be the preferred guest.

Keywords: amides · helical structures · host–guest systems · molecular recognition · supramolecular chemistry

Introduction

Helically folded oligomers and polymers are currently objects of considerable interest. A potentially useful application of these helices is molecular endo-recognition: the hollow of a helix is sometimes large enough to accommodate guest molecules.[1] In recent years, helical structures that recognize saccharides[2] or small hydrophobic molecules,[3] or which bind to water[4,5] or to organic[6] and inorganic cations[7] within an inner cavity have been described. Some helices can also channel metal ions in their hollow through biological membranes.[8] In other systems, the helical conformation occurs only on binding to small molecules or ions,[9] as is the case for helicates.[10] The three-dimensional structure of these host molecules emerges from a dynamic folding process governed by backbone rigidity, intramolecular noncovalent interactions, solvophobic effects, and/or intermolecular noncovalent interactions with their guests. Thus, the self-organized nature of these folded architectures sharply contrasts with the preorganized character of traditional synthetic receptors such as macrocycles.[1]

The binding of a guest molecule to a helical host may occur on simple penetration into the helix hollow through its openings. It may also require temporary unfolding of the helix. A compelling illustration of such a phenomenon has been provided by Moore et al., who designed a guest having the shape of a thin rod complementary to the hollow of a helically folded oligomer, and functionalized each end of

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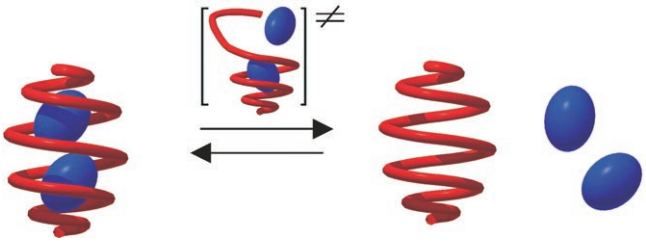
the rod with bulky groups that are too large to enter the hollow.[3b] For binding to occur, the helix thus has to unwind and rewind around the rod. When large conformational changes of the host occur on binding of the guest, major spectroscopic changes may be expected and may prove useful for developing sensors.[7b] For example, association of racemic helices with chiral guests gives rise to strong induced circular dichroism due to a preferred helical handedness of the host in the presence of the guests (i.e., the conversion of a number of helices of a given handedness to helices of the opposite handedness).[2,3,11]

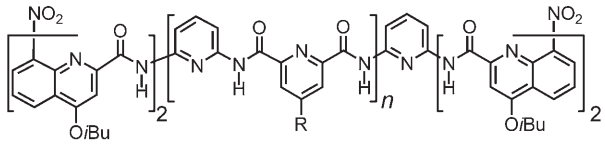
This paper deals with the concept that the two ends of a helix hollow may be capped so as to define a confined space in which guests can be completely secluded from the surrounding medium (Scheme 1). The binding and release of the guests consequently imply a conformational change of the host to temporarily create a passage to and from the binding site. This concept is a novel approach toward molecular encapsulation.



Scheme 1. Encapsulation of egg-shaped guests by a helix with a reduced diameter at both ends via partial unfolding.

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 potential applications in molecular recognition and catalysis,[12] and because of the new insights it gives into otherwise unstable guest species protected from degradation within a secluded environment.[13] Several strategies are available to create a closed shell around a cavity. On the one hand, unimolecular capsules may consist of polymacrocyclic structures[12a,14] or of deep bowl-shape molecules with a bulky rim.[15] On the other hand, capsules may be formed by self-assembly of several molecular components. Examples of the latter category illustrate the numerous possibilities to divide the surface of a sphere[12d,e] (e.g., two hemispherical halves,[16] two nonhemispherical parts,[17] four quarters[18]) or of a polyhedron[12b,c] (e.g., tetrahedron,[19] icosahedron,[20] snub cube,[21] triangular prism[22]) into complementary elements. In contrast, the original approach to molecular capsules that we present here exploits the possibility of tuning the diameter of a helically folded oligomer according to the nature of the monomer units and their position in the oligomer sequence. If the helix diameter is large at the center and reduced at both ends, so that the helix has a shape similar to that of the skin of an apple peeled in a helical fashion, it defines a closed shell and can encapsulate guest molecules on unfolding and refolding, just like an apple peel can be wrapped back around the apple.

Helices derived from aromatic oligoamides (AOAs) are particularly well suited to elaborate helical capsules 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.[4,5,23–25] Hollows as large as 3 nm[24] have been reported by Gong. et al. On the contrary, the highly polar hollow of oligoamides of 2,6-diaminopyridine and 2,6-pyridinedicarboxylic acid are much smaller (ca 0.5 nm), and have been shown to accommodate water both in solution and in the solid state.[4] Other oligoamides, such as those derived from 8-amino-2-quinolinecarboxylic acid, form very stable helices with a hollow too small to accommodate any guest,[25] and therefore are ideal candidates for capping the ends of a helix. In a preliminary communication,[5] we have shown that the short heptameric sequence **1** encapsulates one water molecule both in the solid state and in solution. We now describe the design, synthesis, and



1 *n* = 1, R = OBn
2 *n* = 2, R = O*i*Bu
3 *n* = 3, R = H

solid-state and solution characterization of the binding properties of nonameric and undecameric oligomers **2** and **3**, which have five and seven pyridine units, respectively, and which were thus expected to have larger cavities. In particular, we show that **3** can accommodate up to two water molecules or slightly larger polar guests such as methanol, hydrazine, formic acid, or hydrogen peroxide. These results demonstrate the modularity of the helical capsule concept: the size and cavity of the capsules can, in principle, be tuned at will depending on the nature and number of monomers introduced in the sequence.

Results and Discussion

Design principles: The main purpose of this study was to demonstrate that the helical-capsule concept should in principle give access to cavities of tunable size and properties. Sequences **2** and **3** were selected as relatively easy synthetic targets that would have cavities larger than that of prototype **1**. As shown in Figure 1, energy minimizations and estimations of the inner volumes of the three helical oligomers (see Experimental Section) suggest that the helix cavities should increase in size and progressively shift from a "spherical" to a "cylindrical" shape as the number of pyridine rings in the sequence increases. The diameter of the cylinder is determined by the hollow of the pyridinecarboxamide

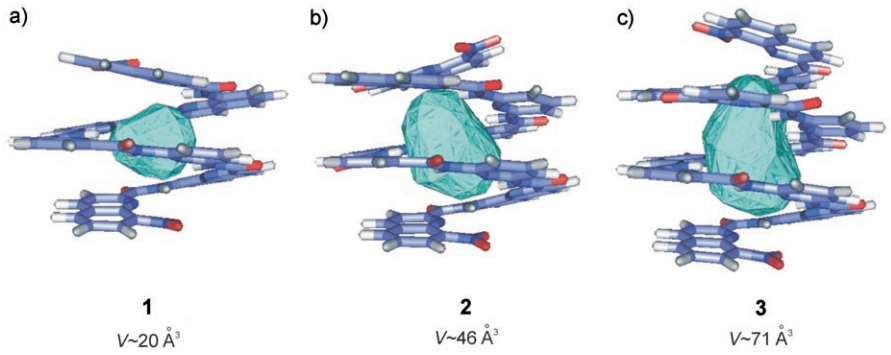
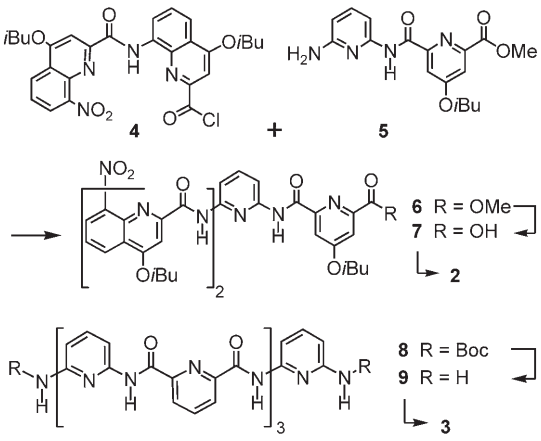


Figure 1. Energy-minimized conformations (MM3 in Macromodel) of left-handed helical oligomers **1**–**3** comprising central pyridine units that create an inner hollow of adjustable length and peripheral quinoline units that cap both ends of this hollow. The inner cavities of the helices are shown in light blue. Estimations of the corresponding inner volumes *V* are indicated below. Isobutoxy and benzyloxy side chains were omitted for the calculations.

oligomers, while its length is determined by the number of pyridine rings in the sequence.

Synthesis: The convergent synthetic paths to nonameric strand **2** and undecameric strand **3** are depicted in Scheme 2. The syntheses appear to be relatively short because they involve previously described precursors that nevertheless require several steps for their preparation. Thus, quinoline dimer acid chloride **4**[25] was coupled to dimeric pyridine amine **5**[11] to give tetrameric intermediate **6** that constitutes the conical ends of a capsule (yield 80%). The ester terminal group of this tetramer was saponified (yield 85%) and the corresponding acid was coupled to an excess of 2,6-diaminopyridine to provide an unstable pentamer amine intermediate which was again treated with **7** to afford **2** (yield 18%). The two Boc-protected amino groups of heptameric pyridine oligomer **8**[26] were deprotected quantitatively with trifluoroacetic acid (TFA) to give oligomer **9**, which reacted with two equivalents of **4** to yield **3** (yield 35%).



Scheme 2. Synthesis of **2** and **3**.

Solid-state studies: Five of the oligomers relevant to this study were characterized by single-crystal x-ray crystallography (Table 1): helical capsules **1**,[5] **2** and **3**, as well as conical tetramer **6** and pyridinecarboxamide heptamer **9**. All show the single helical confor-

Table 1. Crystallographic parameters for **2**, **3**, **6**, **9**.

	2	**3**	**6**	**9**
formula	$C_{93}H_{91}N_{19}O_{18}\cdot 1.57\,C_7H_{16}\cdot C_6H_6\cdot H_2O$	$C_{97}H_{83}N_{23}O_{18}\cdot 2\,C_3H_7NO)\cdot 2\,H_2O$	$2\,C_{45}H_{46}N_8O_{10}\cdot 3\,CHCl_3$	$0.5\,C_{44}H_{39}N_{15}O_8\cdot 0.5\,CH_3OH$
M_r [g mol^{-1}]	2023.30	2041.09	4151.80	905.90
crystal size [mm]	0.20×0.08×0.04	0.20×0.20×0.10	0.50×0.50×0.20	0.15×0.10×0.10
color	yellow	yellow	yellow	colorless
crystal system	triclinic	triclinic	triclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$C2/c$
Z	2	2	2	4
a [Å]	15.4753(5)	13.4000(4)	13.44330(10)	15.7632(15)
b [Å]	17.2696(2)	18.9513(6)	19.2509(2)	15.5898(14)
c [Å]	22.8860(4)	19.8827(5)	20.8616(2)	15.9840(16)
α [°]	66.493(10)	86.711(4)	114.8082(5)	90.00
β [°]	71.498(10)	75.133(3)	92.1876(4)	100.484(7)
γ [°]	85.494(10)	85.082(4)	92.8996(5)	90.00
V [Å^3]	5310.7(2)	4858.9(2)	4883.87(8)	3862.4(6)
ρ [g cm^{-3}]	1.265	1.395	1.412	1.558
T [K]	296(2)	163(2)	150(2)	153(2)
radiation	$Cu_{K\alpha}$	$Cu_{K\alpha}$	$Mo_{K\alpha}$	$Cu_{K\alpha}$
λ [Å]	1.54180	1.54178	0.71073	1.54180
scanned θ [°]	6.40–50.43	6.40–58.93	3.04–26.37	7.34–68.23
total/unique refl.	10163/9367	13128/12655	19929/13102	3353/293
GOF	1.128	1.165	1.058	1.077
R_1 [$I>2\sigma(I)$]	0.1101	0.0690	0.0915	0.1491
CCDC ref.	645200	645198	645197	645199

mation expected on the basis of their sequence, and all but **6** include water or methanol molecules in the polar helix hollow. The top view of the 1.5-turn helical structure of tetramer **6** (Figure 2) clearly illustrates how the terminal quinoline unit, and especially its nitro group, lie over the inner space delineated by the pyridine units.

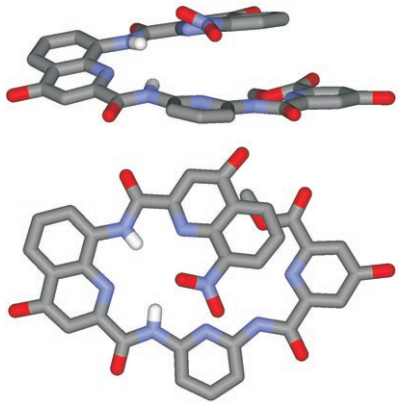


Figure 2. Side and top views of the crystal structure of **6**. Included solvent molecules, isobutyl side chains, and non-amide hydrogen atoms have been omitted for clarity.

Several views of the crystal structures of capsules **1**–**3** are shown in Figure 3. All three structures closely match the energy-minimized models shown in Figure 1 and span 2, 2.5, and 3 helical turns, respectively. They have an inner cavity isolated from the surrounding medium on the sides by the helix wall and on the top and bottom by the faces of the terminal quinoline units. The size of the cavity increases with increasing number of pyridine rings. In all three cases, the cavity is filled by water molecules: one in **1** and **2**, and two in **3**. When the helices are represented as van der Waals spheres, the water molecules cannot be seen either from the side or from the top (not shown) of the capsules. The binding of the guest molecules in the capsule cavities therefore requires a temporary conformational change of the helical architecture (Scheme 1). The X-ray data of **1** and **3** were good enough to localize the hydrogen atoms of water. In all cases, the oxygen atom lies close to the inner wall of the capsule and is doubly hydrogen bonded to the amide protons of a 2,6-pyridinedicarboxamide unit (Figure 4). Depending on the water molecule considered, the hydrogen

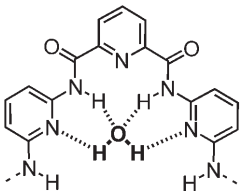


Figure 4. Hydrogen-bonding motif of water molecules in a helix hollow.

bond length d_{NO} varies from 2.84 to 3.17 Å. Since **1**, **2**, and **3** have one, two, and three 2,6-pyridinedicarboxamide units, respectively, one might have expected that they all correspond to water-binding sites and that these numbers of water molecules would have been encapsulated. In fact, binding sites for water molecules that are contiguous in the sequence appear to be too close in space to accommodate water molecules simultaneously. Consequently, oligomer **2** has two binding sites for water molecules but can bind only one at a time, and it can thus be considered as a degenerate receptor relative to **1**. Similarly, the cavity of **3** binds two water molecules and can in principle do so in several ways. Fortunately, however, these degenerate binding modes did not give rise to crystallographic disorder that would have made it difficult to accurately characterize the organization of water in the capsules.

The observation that oligomer **3** hosts two water molecules in the solid state led to speculation that, after releasing water, it might bind slightly larger molecules as well. Evidence for this was provided by the crystal structure of heptameric pyridinecarboxamide oligomer **9**, which constitutes the central sequence of undecamer **3**. In contrast to all other crystal structures that we obtained for pyridine oligomers,[4,11,26] the structure of **9** (Figure 5) shows a methanol molecule completely included in the helix hollow. The methanol oxygen atom is doubly hydrogen bonded to the central 2,6-pyridinedicarboxamide unit, but it statistically occupies two positions slightly above or slightly below the pyridine plane, which leads to some crystal disorder.

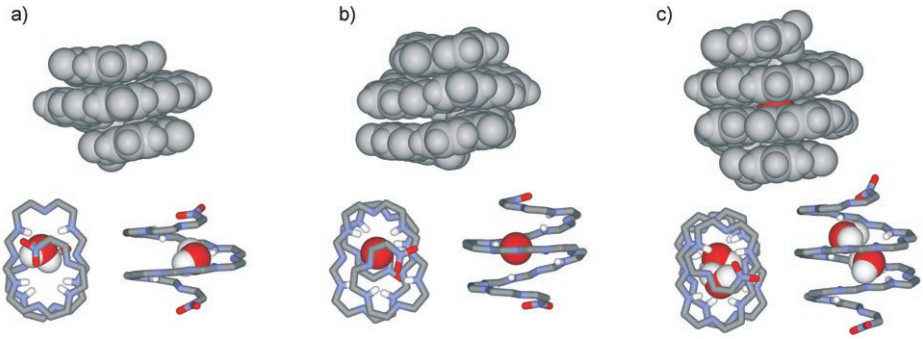


Figure 3. Crystal structures at the same scale of a) **1**, b) **2**, and c) **3**. Side chains and solvent molecules have been omitted for clarity. The top structures show CPK representations of the helices, which completely surround encapsulated water molecules. Bottom structures show tube representations of the inner rim of the helices and encapsulated water molecules as CPK models. Water hydrogen atoms could not be located in b).

Solution studies: To demonstrate that encapsulation as observed within the helices in the solid state is not merely inclusion whereby small molecules simply fill available void space, the ability of **1**–**3** to host water or other guests was investigated in solution by NMR spec-

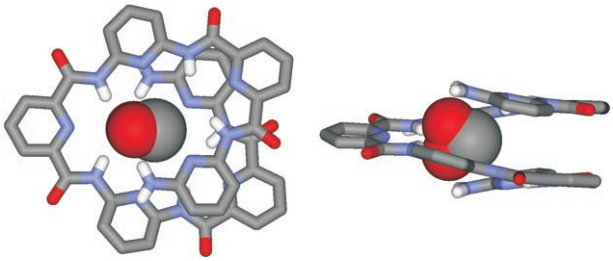


Figure 5. Crystal structure of **9** showing a methanol molecule in the helix hollow. Carbon-bonded hydrogen atoms have been omitted for clarity. The methanol oxygen atom occupies two statistical positions.

troscopy. The behavior of **1** has already been reported[5] and only salient characteristics will be recalled here: 1) NMR spectra show all the features of folded helices characterized for oligomers comprising only pyridine[4,11,26] or only quinoline[25] 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 π–π stacking); 2) the ^{1}H NMR signals of the central amide units (and only these signals) undergo strong downfield shifts ($\Delta\delta = 1.5$ ppm) with increasing water concentration in $CDCl_3$ or with decreasing temperature at a given concentration due to hydrogen bonding with the encapsulated water molecule; 3) the central amide signals undergo much faster chemical exchange with water protons than the peripheral amide units; 4) at low temperature, binding and release of water is slow on the NMR timescale and distinct signals are observed for the full and empty capsule and for free and bound water.

The NMR investigations showed that **2** also binds one water molecule in solution, as it does in the solid state. The main difference to **1** is that **2** is a degenerate receptor with two binding sites (i.e., two 2,6-pyridinedicarboxamide units) of which only one at a time can be occupied. The 1:1 stoichiometry of the $H_2O\subset$**2** complex was established by monitoring the ^{1}H NMR signal of the bound water molecule that appears at low temperature (Figure 6). The included water molecule gives a signal at $\delta = 4.70$ ppm at $-55\,^\circ$C, which compares with $\delta = 4.41$ ppm for $H_2O\subset$**1** at the same temperature. Both values reflect the high polarity of the capsule cavities as the focal point of amide protons and pyridine nitrogen atoms. In both cases, integration of the signal for included water unambiguously indicated 1:1 stoichiometry of the complex.

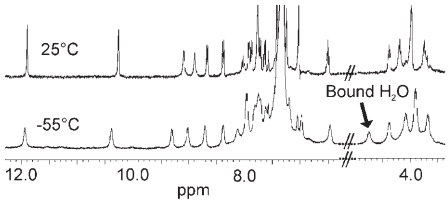


Figure 6. Part of the 400 MHz ^{1}H NMR spectra of **2** in $CDCl_3$ showing the signal of a bound water molecule at $-55\,^\circ$C.

On cooling a solution of **2** in $CDCl_3$, the two ^{1}H NMR signals assigned to its four central amide protons undergo downfield shifts as an increasing number of capsules bind (i.e., form hydrogen bonds) to water (Figure 7). In comparison, the signal at 11.9 ppm assigned to the most peripheral amide protons (between the two quinoline units) shifts very little ($\Delta\delta < 0.1$ ppm), in agreement with the solid-state structure, which suggests that these protons do not interact with encapsulated water. Above 0 °C, the full and empty capsules exchange rapidly on the NMR timescale and averaged signals are observed. Below this temperature, exchange becomes slow and two sets of signals for the empty and for the full capsule are expected. However, because of the insufficiently low water content of the sample[27] and the low temperature, all capsules are occupied by a water molecule and only one set of temperature-independent signals corresponding to $H_2O\subset$**2** is observed

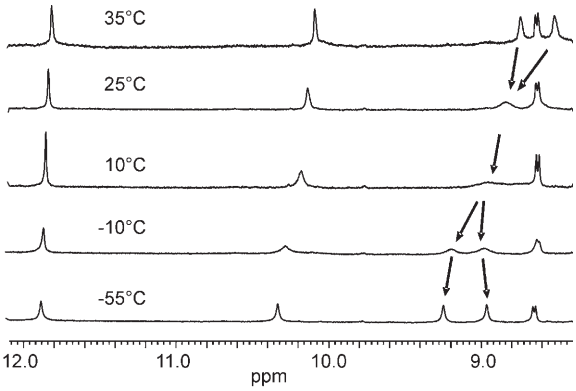


Figure 7. Part of the 400 MHz ^{1}H NMR spectra of **2** in $CDCl_3$ showing amide resonances at various temperatures.

The largest chemical shift difference between the amide signals of full and empty **2** is 0.7 ppm. This maximum $\Delta\delta$ value is smaller (by about half) than that observed in the NMR spectra of **1** ($\Delta\delta = 1.6$ ppm). This is likely the result of the degeneracy of the binding sites in **2**: at a given time, only one site forms hydrogen bonds with water and the other is unoccupied. Interestingly, even at $-55\,^\circ$C, the spectra of **2** reflect an average C_2 symmetry of the $H_2O\subset$**2** complex, which indicates that the encapsulated water molecule hops rapidly from one site to the other. The degeneracy of water binding in **2** may in principle give rise to a binding constant to water K_a twice as large for **2** than for **1**. However, this proved difficult to verify because of the poor accuracy of estimating binding constants based on the chemical shift variations of the amide NMR signals and integration of the water signal. Both constants are on the order of 100–200 L mol^{-1}.

Similar investigations were carried out with the largest capsule **3**, and again the solution data proved to be consistent with those obtained in the solid state. At low temperature, three different sets of capsule signals were observed in the ^{1}H NMR spectra of **3** in $CDCl_3$ depending on the water

content of the sample. All sets coalesce to one on heating. If more than two equivalents of water are present (not shown), only one species is observed that corresponds to the capsule with two water molecules $(H_2O)_2\subset$**3**. If more than one but less two equivalents of water are present, two species are observed: $(H_2O)_2\subset$**3** as above, while the other was assigned to the capsule with one water molecule $H_2O\subset$**3** (Figure 8b). If less than one equivalent of water is present, two sets of signals are again observed, one corresponding to $H_2O\subset$**3** and the other to the empty capsule **3**. As expected, the resonances of amide groups that can form hydrogen bonds to encapsulated water shift downfield from empty **3** to $H_2O\subset$**3** and further downfield to $(H_2O)_2\subset$**3**. Despite all our efforts, we could never observe the three species simultaneously. It seems that $(H_2O)_2\subset$**3** appears only when all capsules already host one water molecule, and this suggests some negative cooperativity between the first and second water-binding events.

The stoichiometry of these complexes was easily confirmed by monitoring the integration of the signals of the encapsulated water molecules (Figure 9). When one water molecule is encapsulated, its signal appears at $\delta = 4.50$ ppm. When two water molecules are encapsulated, they appear at $\delta = 5.26$ ppm as a single signal, that is, unlike in the crystal, they are equivalent on average even at low temperature. Conversely, the spectra reflect an average C_2 symmetry of the $H_2O\subset$**3** and $(H_2O)_2\subset$**3** complexes, that is, the encapsulated water molecule(s) hop(s) rapidly from site to site, though two water molecules are unlikely to swap positions without partial unfolding of the helix.

The kinetics of binding and release of water molecules are slower for longer capsule **3** than for **1** and **2**. Indeed, the coalescence temperature of the amide signals of **3** and $H_2O\subset$**3** is 25°C, which compares to 0°C and −10°C for **2** and $H_2O\subset$**2**, and **1** and $H_2O\subset$**1**, respectively. This is consistent with increasing stability of the helical conformation with increasing number of helical turns, as described previously.[4a] It suggests that even larger capsules for larger guests may undergo very slow kinetics that could be useful for implementing controlled release of the guests.

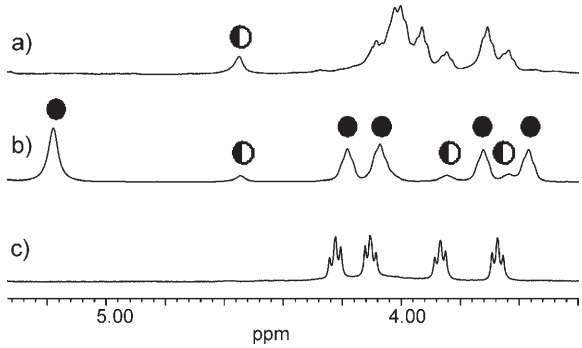


Figure 9. Part of the 400 MHz ^{1}H NMR spectra of **3** in $CDCl_3$ showing encapsulated-water resonances (at $\delta = 4.50$ and 5.26 ppm) and the resonances of the CH_2 group of the isobutoxy chains (at $\delta = 3.5$–4.3 ppm): a) at −40°C in the presence of less than one equivalent of H_2O, b) at −40°C in the presence of more than one equivalent of H_2O, and c) at 25°C. The half-filled circles and black circles indicate signals assigned to $H_2O\subset$**3** and $(H_2O)_2\subset$**3**, respectively.

Given the ability of **3** to host two water molecules in solution and of its central section **9** to host one methanol molecule in the crystal (Figure 5), we investigated binding of **3** with several small polar guests larger than water (i.e., bearing two or three non-hydrogen atoms): hydrazine, methanol, hydrogen peroxide, and formic acid (Figure 10). In the case of methanol and formic acid, the general trend is that when water is abundant in the sample, the only species observed at low temperature by ^{1}H NMR is the doubly hydrated capsule $(H_2O)_2\subset$**3**. When care is taken to remove water by distilling the guest and $CDCl_3$ and by azeotropic distillation of the capsule with anhydrous toluene, new species (different in each case) appear in the NMR spectra, in slow exchange with the hydrated capsule (Figure 10b and d). New species also appear in the case of hydrazine and hydrogen peroxide even if no care is taken to remove water from the samples; these guests were were in fact added as hydrates.

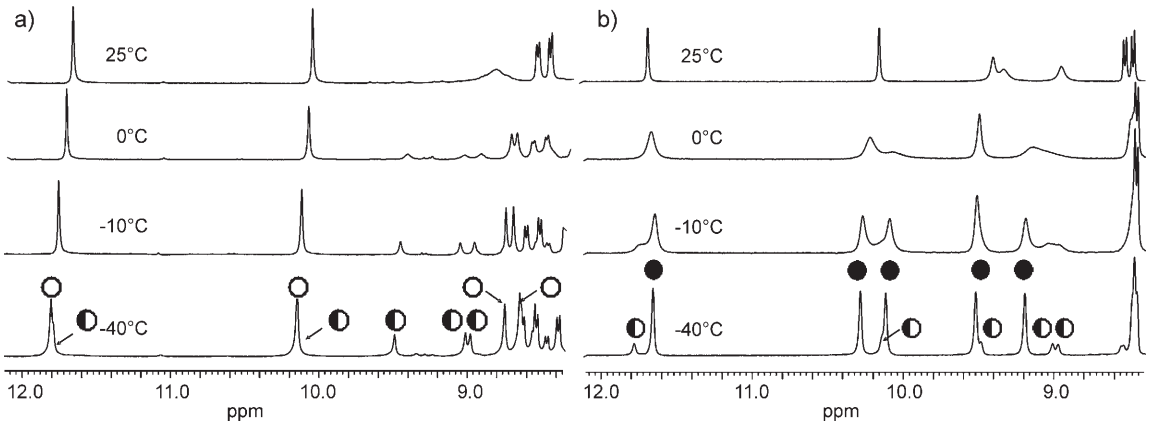


Figure 8. Part of the 400 MHz ^{1}H NMR spectra of **3** in $CDCl_3$ showing amide resonances at various temperatures: a) in the presence of less than one equivalent of H_2O and b) in the presence of more than one equivalent of H_2O. The white circles, half-filled circles, and black circles indicate signals assigned to empty **3**, $H_2O\subset$**3**, and $(H_2O)_2\subset$**3**, respectively.

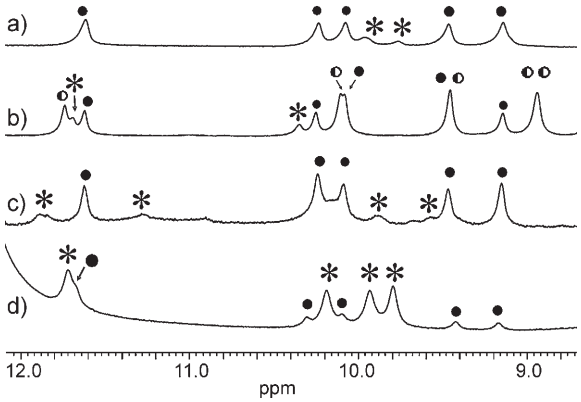


Figure 10. Part of the 400 MHz ^{1}H NMR spectra of **3** at −40 °C in $CDCl_3$ showing amide resonances in the presence of an excess of a) NH_2NH_2, b) MeOH (50 equiv), c) H_2O_2, d) formic acid (22 equiv). The half-filled circles and black circles indicate signals assigned to $H_2O\subset$**3** and $(H_2O)_2\subset$**3**, respectively. The stars indicate signals assigned to the capsule hosting one polar guest other than water.

These new species were assigned to capsules containing a guest other than water. Based on the inner volume observed in the solid state, methanol, hydrazine, hydrogen peroxide, and formic acid can all be accommodated without significant distortion of the helical conformation of **3**. When similar experiments were carried out with the smaller capsules **1** and **2**, no species other than the hydrate was observed, except when hydrogen peroxide was used as a guest with **2** (not shown).

In the case of hydrazine, methanol, and formic acid, it seems unlikely that the complexes observed with **3** correspond to the simultaneous encapsulation of one polar guest plus one water molecule, though this hypothesis could not be completely ruled out on the basis of experimental data. In the case of hydrogen peroxide, the number of new signals in the presence of the guest allows one to hypothesize the presence of more than one new species. In addition to $H_2O_2\subset$**3**, $(H_2O,H_2O_2)\subset$**3** or $(H_2O_2)_2\subset$**3** can be envisaged. All attempts to identify the complexes by mass spectrometry (ES or MALDI) were unsuccessful: only the empty capsule was observed.

Unfortunately, no reliable quantitative analysis of the binding events could be performed in the presence of the larger guests due to the difficulty of simultaneously evaluating the amounts of bound and unbound water. However, some qualitative conclusions can be drawn. Among the four guests tested, binding to methanol and formic acid are the least favorable. Even in the presence of an excess of methanol, some monohydrated capsule $H_2O\subset$**3** is observed, and with both guests, only the hydrated species are observed unless a large excess of methanol or formic acid is used. This is possibly due to the lower polarity of methanol and larger size of formic acid. In contrast, hydrazine and hydrogen peroxide were added to the samples as hydrates, but their encapsulation nevertheless occurred. These two guests are thus apparently able to compete with water. The encapsulation of hydrogen peroxide is of particular interest given the poor stability of this compound in the absence of water and its use as an oxidizing agent. In this respect, it is interesting that hydrogen peroxide does not *N*-oxidize the central 2,6-diaminopyridine units in capsules **2** and **3**. This contrasts with our previous report that such units are easily and selectively oxidized when they are located at the end of a helical oligomer and when a stronger oxidizing agent (*m*-chloroperbenzoic acid) is used.[28]

Conclusion

In summary, both solid-state and solution studies show that progressively increasing the size of the helical capsules by including additional monomers in the center of their sequence allows their binding properties to be tuned in a modular fashion. More guests or larger guests can be included when the capsule size is rationally increased. Even though the guests studied here are small, these findings open the prospect of elaborating even larger capsules by incorporating monomers that code for an even larger helix diameter. It also appears from our studies that water is a preferred guest molecule in the hollow of the smaller capsules based on aza-aromatic amide oligomers. However, it can be anticipated that capsules with larger cavities will prefer to accommodate larger guests rather than a large number of water molecules for obvious entropic reasons. It is also possible that guests of other types, such as phosphate or sulfate anions, would be preferred to water because they are involved in stronger interactions. So far, the binding and release of guest molecules is considerably slowed down by the units that close the capsule ends but remains fast on the NMR timescale at 25 °C. This implies characteristic exchange times of less than 100 ms, which would be too fast to use the capsules as containers for controlled release of guests. However, we find that increasing helix length results in slower guest release and speculate that larger guests may escape more slowly: controlled guest release may thus be a potential application of advanced prototypes of molecular apple peels.

Experimental Section

General: All reactions were performed in oven-dried glassware under a slight positive pressure of nitrogen. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million relative residual solvent peaks. Infrared (IR) spectra were recorded on a Mattson Satellite (ATR) FTIR.

Tetramer 6: Quinoline dimer acid chloride **4**[25] was prepared from the corresponding carboxylic acid (110 mg, 207 μmol) by reaction with thionyl chloride (0.75 mL, 10.3 mmol, 50 equiv). The solution was heated at reflux for 5 min, and then thionyl chloride was removed under vacuum. The solid was dissolved in dry dichloromethane (2 mL), and diisopropylethylamine (72 μL, 414 μmol, 2 equiv) and pyridine dimer **5**[11] (71 mg, 217 μmol, 1.05 equiv) were added to the solution. The reaction mixture was stirred at room temperature for 12 h. The solution was washed with water. The organic phase was dried over $MgSO_4$, filtered, and concentrat-

ed. The residue was purified by column chromatography on silica gel with $CHCl_3$ as eluent to give tetramer **6** (142 mg, 80% yield) as a yellow powder. Single crystals for X-ray diffraction analysis were obtained by slow liquid–liquid diffusion of heptane into a chloroform solution (see Table 1 and Figure 2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.19 (s, 1H), 10.51 (s, 1H), 9.41 (s, 1H), 8.96 (d, J(H,H) = 7.6 Hz, 1H), 8.18 (d, J-(H,H) = 7.6 Hz, 1H), 8.09 (d, 1H, J(H,H) = 7.6 Hz), 8.05–8.02 (m, 3H), 7.94 (s, 1H), 7.92–7.85 (m, 2H), 7.81 (s, 1H), 7.74 (s, 1H), 7.67 (t, J-(H,H) = 7.6 Hz, 1H), 6.96 (t, J(H,H) = 7.6 Hz, 1H), 4.16–4.11 (m, 4H), 3.96 (d, J(H,H) = 6.4 Hz, 2H), 2.35–2.17 (s, 3H), 1.17 (d, J(H,H) = 6.4 Hz, 12H) 1.10 ppm (d, J(H,H) = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.6, 164.5, 163.6, 163.4, 162.7, 162.1, 161.2, 153.8, 151.1, 149.8, 149.6, 148.9, 148.0, 145.5, 140.5, 139.8, 138.9, 134.2, 127.6, 127.2, 127.2, 124.67, 123.5, 122.4, 118.8, 116.9, 114.6, 110.9, 110.9, 110.0, 99.5, 99.2, 75.8, 75.3, 52.6, 28.2, 28.1, 28.0, 19.2, 19.0 ppm.

Capsule 2: Tetramer **6** (488 mg, 569 μmol) was dissolved in THF/H_2O (4/1, 250 mL). NaOH (455 mg, 11.4 mmol, 20 equiv) was added to the solution. The reaction mixture was stirred for 2 h at 25°C. The solution was acidified with acetic acid and solvents were removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residual solid was purified by column chromatography on silica gel eluting with $CHCl_3$ to give tetramer acid **7** (412 mg, 85% yield) as a yellow powder which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.05 (s, 1H), 10.49 (s, 1H), 9.81 (s, 1H), 9.06 (d, J(H,H) = 7.6 Hz, 1H), 8.41 (d, J(H,H) = 8.0 Hz, 1H), 8.23–8.16 (m, 3H), 8.06 (d, J(H,H) = 8.0 Hz, 1H), 7.98–7.90 (m, 2H), 7.82 (s, 2H), 7.69 (t, J-(H,H) = 8.0 Hz, 1H), 7.29–7.25 (m, 2H), 4.18 (d, J(H,H) = 6.4 Hz, 2H), 4.14 (d, J(H,H) = 6.4 Hz, 2H), 3.91 (d, J(H,H) = 6.4 Hz, 2H), 2.40–2,10 (m, 3H), 1.19–1.16 (m, 12H), 1.06 ppm (d, J(H,H) = 6.4 Hz, 6H). Compound **7** (44 mg, 52 μmol) and freshly sublimed 2,6-diaminopyridine (28 mg, 260 μmol, 5 equiv) were dissolved in 2 mL of dry dichloromethane. Triethylamine (14 μL, 104 μmol, 2 equiv) and 5-chloro-1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium-3-oxide hexafluorophosphate (HCTU, 214 mg, 521 μmol, 4 equiv) were then added. The mixture was stirred for three days at 25°C. Every day, additional HCTU (214 mg, 521 μmol, 4 equiv) was added to the mixture. The solvent was removed and the residue was purified by column chromatography on silica gel with $CHCl_3$ as eluent to give 22 mg of an unstable mono amine intermediate (mono adduct product) as a yellow powder. This pentameric oligomer (22 mg, 24 μmol) was dissolved in dry dichloromethane (2 mL) and then **7** (44 mg, 52 μmol, 8 equiv), HCTU (214 mg, 521 μmol, 8 equiv), and triethylamine (14 μL, 104 μmol, 8 equiv) were added. The mixture was stirred for 3 d at 25°C and every day additional HCTU (214 mg, 521 μmol, 4 equiv) was added. The solvent was removed and the residue purified by column chromatography on silica gel with $CHCl_3$ as eluent to give capsule **2** (18 mg, yield 18%) as a yellow powder. Single crystals for X-ray diffraction analysis were obtained by slow liquid–liquid diffusion of heptane into a toluene solution (see Table 1 and Figure 3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.83 (s, 2H), 10.25 (s, 2H), 9.15 (s, 2H), 8.96 (s, 2H), 8.60 (d, J(H,H) = 7.2 Hz, 2H), 8.33 (d, J(H,H) = 7.6 Hz, 2H), 7.97 (t, J(H,H) = 8.0 Hz, 1H), 7.88 (d, J(H,H) = 5.2 Hz, 2H), 7.81 (d, J(H,H) = 7.2 Hz, 2H), 7.75–7.65 (m, 9H), 7.58 (d, J(H,H) = 8.0 Hz, 2H), 7.39 (s, 2H), 7.31–7.25 (m, 3H), 7.19 (s, 2H), 6.98 (s, 2H), 6.46 (t, J(H,H) = 8.0 Hz, 2H), 4.34–4.30 (m, 2H), 4.17–4.11 (m, 2H), 3.93–3.89 (m, 4H), 3.70–3.65 (m, 4H), 2.43–2.09 (m, 6H), 1.48–1.05 ppm (m, 36H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.4, 163.1, 162.6, 161.4, 161.2, 160.5, 159.3, 153.1, 149.4, 148.9, 148.7, 148.3, 148.0, 147.9, 144.1, 140.8, 140.6, 139.7, 137.7, 133.8, 127.7, 127.4, 127.1, 123.8, 123.3, 121.5, 117.5, 116.0, 110.7, 110.6, 109.9, 109.9, 109.5, 99.8, 98.6, 75.6, 75.3, 75.1, 30.9, 29.7, 29.3, 28.3, 28.2, 28.0, 19.4, 19.3, 19.2 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 3165, 2963, 2251, 1780, 1461, 1378, 1319, 1089, 1038, 921 cm^{-1}; MS (TOF-MS ES+): *m/z* calcd for $[M+H]^+$ ($C_{93}H_{91}N_{19}O_{18}$): 1762.68; found: 1762.54.

Capsule 3: Heptamer **8**[26] (40 mg, 48 μmol) was dissolved in CH_2Cl_2/TFA (3/1, 4 mL). The solution was stirred for 2 h at 25°C. All volatiles were removed to give diamine **9** (32 mg, quantitative yield) as a white powder, which was used without purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.78 (s, 2H), 11.43 (s, 2H), 10.98 (s, 2H), 8.50 (d, J(H,H) = 7.6 Hz, 2H), 8.99 (t, J(H,H) = 7.2 Hz, 3H), 8.30 (t, J(H,H) = 7.6 Hz, 2H), 8.17 (d, J-(H,H) = 7.6 Hz, 2H), 8.01–7.93 (m, 4H), 7.42 (t, J(H,H) = 8.4 Hz, 2H), 6.74 (d, J(H,H) = 8.0 Hz, 2H), 6.47 ppm (d, J(H,H) = 8.4 Hz, 2H). Crystals were obtained by gas–liquid diffusion of MeOH into a DMF (dimethylformamide) solution. Quinoline dimer acid chloride **4**[25] was prepared from the corresponding carboxylic acid (90 mg, 169 μmol) as described in the preparation of **6**. The acid chloride was dissolved in dry dimethylacetamide (2 mL). Diamine **9** (42 mg, 50 μmol, 0.3 equiv) and triethylamine (90 μL, 676 μmol, 4.0 equiv) were added to the solution. The mixture was stirred at 25°C for 48 h. The solution was diluted with CH_2Cl_2 and the organic phase was washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (98/2) as eluent to give capsule **3** (32 mg, yield 35%) as a yellow powder. Single crystals for X-ray diffraction analysis were obtained by slow liquid–liquid diffusion of Et_2O into a DMF solution (see Table 1 and Figure 4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.16 (s, 2H), 9.73 (s, 2H), 9.45 (s, 2H), 9.07 (s, 2H), 8.41 (t, J-(H,H) = 8.0 Hz, 4H), 8.13–8.06 (m, 4H), 7.86 (d, J(H,H) = 7.6 Hz, 2H), 7.80–7.69 (m, 17H), 7.63 (s, 2H), 7.53 (d, J(H,H) = 8.4 Hz, 2H), 7.21 (s, 2H), 7.14 (t, J(H,H) = 8.0 Hz, 2H), 7.02 (s, 2H), 6.47 (t, J(H,H) = 8.0 Hz, 2H), 4.25 (d, J(H,H) = 7.6 Hz, 1H), 4.24 (d, J(H,H) = 7.6 Hz, 1H), 4.13 (d, J(H,H) = 7.6 Hz, 1H), 4.11 (d, J(H,H) = 7.6 Hz, 1H), 3.81 (d, J-(H,H) = 7.6 Hz, 1H), 3.79 (d, J(H,H) = 7.6 Hz, 1H), 3.64 (d, J(H,H) = 7.6 Hz, 1H), 3.62 (d, J(H,H) = 7.6 Hz, 1H), 2.41–2.17 (m, 4H), 1.28 (d, J-(H,H) = 6.8 Hz, 6H), 1.24 (d, J(H,H) = 6.8 Hz, 6H), 1.14 (d, J(H,H) = 6.8 Hz, 6H), 1.08 ppm (d, J(H,H) = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.0, 162.5, 161.5, 161.2, 160.1, 159.4, 153.3, 148.9, 148.7, 148.0, 147.8, 146.8, 145.4, 144.0, 141.1, 140.7, 139.6, 139.4, 137.5, 133.6, 127.9, 127.5, 127.2, 125.7, 124.6, 124.0, 123.6, 123.4, 121.5, 117.6, 116.3, 110.5, 110.4, 109.5, 109.0, 99.6, 98.9, 77.2, 75.3, 75.2, 28.2, 27.9, 19.3, 19.2 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 3160, 2975, 2885, 1645, 1447, 1409, 1371, 1333, 1085, 1040 cm^{-1}; MS (TOF-MS ES+): *m/z* calcd for $[M+H]^+$ ($C_{97}H_{83}N_{23}O_{18}$): 1858.63; found: 1858.51.

X-ray crystallography: Single crystals of **2**, **3**, and **9** were mounted on a Rigaku R-Axis Rapid diffractometer equipped with a MM007 microfocus rotating-anode generator with monochromatized $Cu_{K\alpha}$ radiation (1.54178 Å). Data collection, unit cell refinement, and data reduction were performed with the CrystalClear software package. The positions of non-H atoms were determined by the program SHELXD, and the position of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined. A single crystal of **6** was mounted on a Bruker-Nonius κ-CCD diffractometer with graphite-monochromatized $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The data collection was based on φ-scans completed by ω-scans. The final unit cell was determined on the basis of all the collected frames. The data reduction was performed by using the COLLECT software (Nonius, 1998). The positions of non-H atoms were determined by the program SHELXD and the positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined. CCDC-645197–CCDC-645200 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.

Molecular modeling: The oligomer conformations were obtained from energy minimization performed with Maestro (v6.5)–Macromodel (v8.6) software.[29] The structures were minimized by using the truncated Newton conjugate gradient (TNCG) method and the MM3* force field to obtain local energy minima. The volumes and shapes of the inner cavities were estimated by using the SURFNET[30] software.

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