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Strained Aromatic Oligoamide Macrocycles as New Molecular Clips

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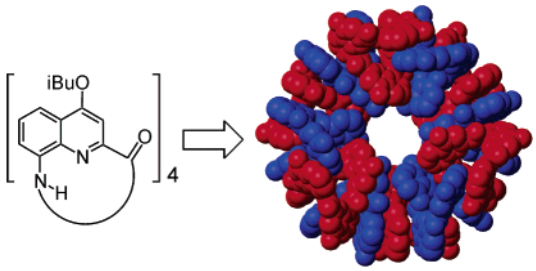
ABSTRACT



Can one join both ends of a helix? A helical aromatic oligoamide was macrocyclized into a saddle-shaped bifunctional clip molecule that self-assembles into discrete circular dodecamers in the solid state and shows great potential for binding aromatic acid guests in solution. The cyclization step requires that the helix is only partly denatured in the reaction medium.

Aromatic−aromatic interactions are ubiquitous in chemical and biological recognition.[1] It is thus not surprising that synthetic host molecules capable of selectively binding aromatic guests have occupied a central position in molecular recognition studies. These systems provide insights in aromatic interactions that may be useful to the design of, e.g., liquid crystals, crystals, or ligands for biological targets.[1] They may also be used as building and/or functional elements in self-assembled nanometer-sized architectures and devices such as those based on rotaxanes.[2] Macrocycles consisting of a cavity surrounded by several aromatic residues such as cyclophanes, calixarenes, or resorcinarenes have proven to be highly versatile receptors for aromatic guests.[1] Other classes of receptors include molecular tweezers that can sandwich aromatic guests between two more-or-less parallel aromatic surfaces attached to a rigid scaffold such as glycouril[3] or Diels−Alder adducts.[4] Here, we report on our serendipitous discovery and preliminary study of a new class of strained aromatic oligoamide macrocycles, obtained by cyclizing helical oligomers, that show great potential for self-assembly and binding of aromatic acid guests.

As we have recently shown, oligoamides of 8-amino-2-quinolinecarboxylic acid **1** adopt unusually stable helical conformations held by a network of hydrogen bonds between amide protons and adjacent quinoline nitrogens and by extensive intramolecular aromatic stacking (Scheme 1).[5,6] To obtain longer strands than those prepared by stepwise synthesis, we recently started to investigate polymerization of monomer **1**. Aromatic amino acids are notoriously difficult

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(4) Klärner, F.-G.; Kahlert, B. *Acc. Chem. Res.* **2003**, *36*, 919−932 and references therein.

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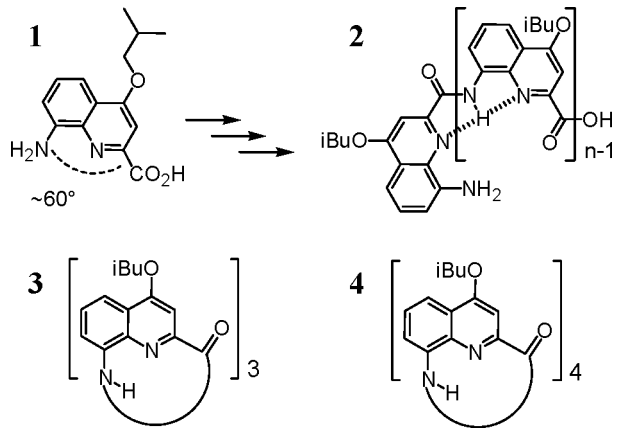
Scheme 1



to polymerize because of the poor nucleophilicity of the amines and extensive intra- and interchain interactions. To alleviate these limiting factors, optimized conditions often require high temperatures and very polar solvents, such as concentrated LiCl (1 M) solutions in NMP and pyridine after activation of the acid with triphenyl phosphite.[7] Unfortunately, mass spectrometry revealed that, even under these conditions, amino acid **1** yields oligomers of only 20 units or less.

In addition to the linear oligomers, cyclo-trimer **3** and cyclo-tetramer **4** can be easily isolated.[8] These cyclic compounds form in significant amounts (20% each) despite the high initial concentration of monomer (0.36 M), which suggests that their formation is directed in one way or another. The structure of trimer **3** in the solid is shown in Figure 1a.[9]

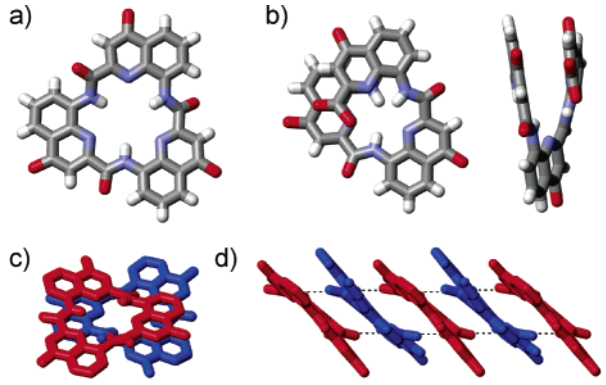


Figure 1. Structures of cyclic trimer **3** (a) and of a trimeric fragment of a longer noncyclic oligomer[5a] (b) in the crystal; views down the [100] axis (c) and down the [011] axis (d) showing the stacks formed by **3**. Isobutyl chains have been omitted for clarity. Dotted lines indicate intermolecular hydrogen bonds.

The macrocycle consists of an almost flat disk that piles up face-to-face in the crystal. Two of the three carbonyl groups protrude slightly above and below the aromatic plane to form a network of intermolecular hydrogen bonds with amide protons (NH···O: 3.2 Å, 154.7°).[10]

The formation of **3** can be understood on the basis that its curvature (corresponding to 3 units per turn) is only slightly lower than the curvature of the noncyclic trimer, shown in Figure 1b, which adopts a helical conformation (corresponding to 2.5 units per turn). The helical trimer is preorganized for cyclization[11] and its ring closure only requires a slight lengthening of intramolecular hydrogen bonds. An illustration of the curvature change between the noncyclic and the cyclic trimer is given by the aspect of the inner rims of the two structures (Figure 1a,b). That of the noncyclic trimer is similar to a pentaaza-15-crown-5 macrocycle, whereas that of **3** is a hexaaza-18-crown-6 macrocycle.

On the other hand, the formation of **4** was not expected. The noncyclic tetramer is a helix extending to over 1.5 turns (Figure 2b) that must be unfolded to allow cyclization. The crystal structure of **4** consists of two similar but independent molecules of which one is shown in Figure 2a.[12] The conformation strongly deviates from planarity and has a saddle shape related to the 1,3-alternate conformation of calix-4-arenes, with two quinoline rings pointing up and two quinoline rings pointing down. The structure of the inner rim of **4** reveals that only two intramolecular hydrogen bonds have been broken during cyclization (double headed arrows in Figure 2a). Moreover, two dihedral angles of near 90° between aryl and amide groups indicate that conjugation is also partially lost. The loss of two hydrogen bonds and the loss of conjugation are probably responsible for some strain in the structure of macrocycle **4**. It is locked in a high-energy state and would undergo a large conformational change to a helix upon ring opening.

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(8) See Supporting Information.

(9) Crystal data for **3**. $C_{42}H_{42}N_6O_6$, M_r = 726.82, crystal size 0.35 × 0.35 × 0.10, Z = 2, triclinic, space group $P\bar{1}$, a = 9.620(2) Å, b = 13.402(2) Å, c = 15.351(3) Å, α = 106.18(2)°, β = 96.31(2)°, γ = 98.80(2)°, U = 1853.9(6) Å^3, ρ_{calc} = 1.302 mg m^{-3}, T = 296(2) K, θ_{min} = 4.71, θ_{max} = 59.96, λ = 1.54180. Radiation type Cu Kα, an empirical absorption correction was applied, μ(Cu Kα) = 0.719 mm^{-1}, T_{min} = 0.7869, T_{max} = 0.9316. Data collected on a CAD4 Enraf-Nonius diffractometer. Of 5470 reflections measured, 5470 were unique. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (SHEXLTL v.6.12). Final R1 = 0.0611 ($I > 2(I)$) and $wR2(F^2)$ = 0.1769 (all data).

(10) The distance is between the two heavy atoms and the angle is the N−H−O angle.

(11) For a recent example see: Becerril, J.; Bolte, M.; Burguete, M. I.; Galindo, F.; García-España, E.; Luis, S. V.; Miravet, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6677−6686.

(12) Crystal data for **4**. $(C_{56}H_{56}N_8O_8)_2C_6H_5Cl(H_2O)_2$, M_r = 2082.73, crystal size 0.20 × 0.20 × 0.07, Z = 18, hexagonal, space group $R\bar{3}$, a = 33.0300(10) Å, b = 33.0300(10) Å, c = 56.600(3) Å, α = 90°, β = 90°, γ = 120°, U = 53477(4) Å^3, ρ_{calc} = 1.156 mg m^{-3}, T = 296(2) K, θ_{min} = 2.94, θ_{max} = 20.00, λ = 0.71073. Radiation type Mo Kα, a semiempirical absorption correction was applied, μ(Mo Kα) = 0.100 mm^{-1}, T_{min} = 0.9802, T_{max} = 0.9930. Data collected on a Nonius KappaCCD diffractometer. Of 33781 reflections measured, 11018 were unique (R_{int} = 0.1334). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (SHEXLTL v.6.12). Final R1 = 0.1258 ($I > 2(I)$) and $wR2(F^2)$ = 0.4137 (all data).

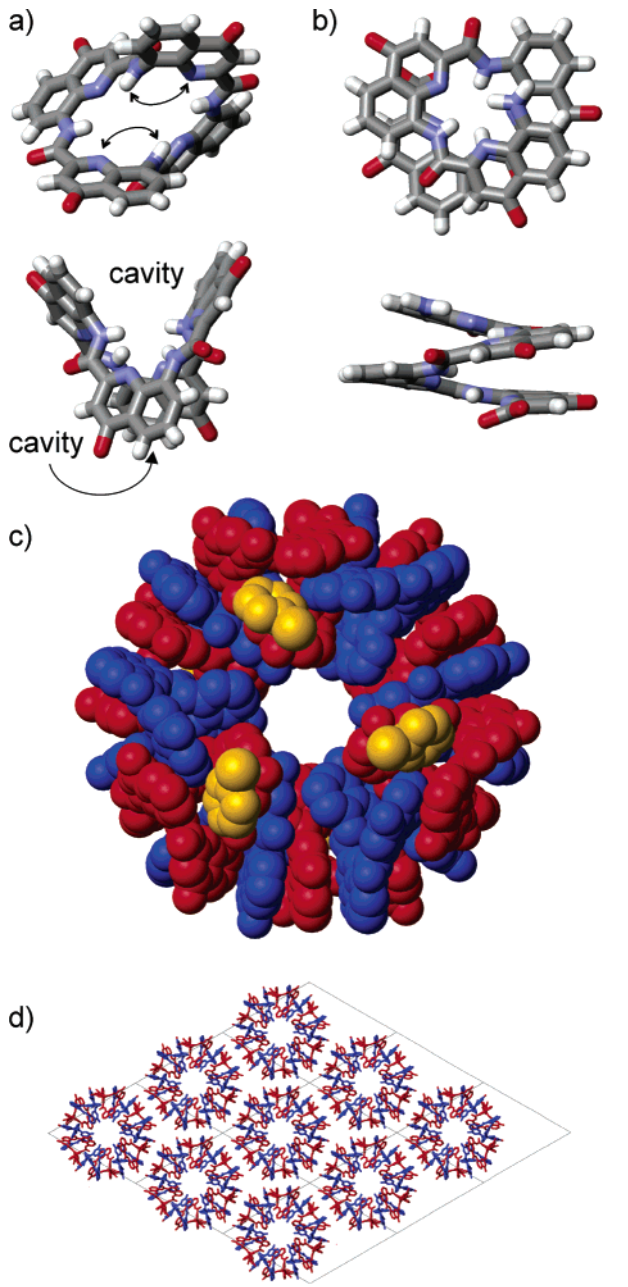

Figure 2. Top views and side views of the structures of cyclic tetramer **4** (a) and of a tetrameric fragment of a longer noncyclic oligomer[5a] (b) in the crystal; top view of a rosette formed from 6 pairs of the two crystallographically independent molecules of four (in red and blue, respectively) and six molecules of chlorobenzene (in yellow); view down the [001] axis of one layer of hexagonally packed rosettes (d). Isobutyl chains and included water molecules have been omitted for clarity.

The polar reaction medium, coordination of Li^+ ions, and high temperature presumably help in overcoming the conformational barriers to the macrocycle, yet without completely denaturing the helical tetramer, which would lead to longer oligomers. When milder polymerization conditions ($PPh_3-C_2Cl_6$ in pyridine)[13] were used only trace amounts of **4** were detected and a large quantity of **3** was isolated (50%).

^{1}H NMR indicates that the four quinoline rings of **4** are equivalent.[8] The macrocycle does not possess any plane or center of symmetry, but has an average S_4 symmetry axis and is thus not chiral. Nevertheless, an analogue of **4** comprising more than one kind of side chain in position 4 of the quinolines would be chiral even if the side chains do not contain any asymmetric center. The methylene protons of the isobutyl side chains of **4** give rise to diastereotopic motifs.[8] Coalescence between these signals should occur when the two degenerate conformers of **4** exchange rapidly upon flipping up the two quinoline rings which point down and flipping down the two quinoline rings which point up. However, no coalescence is observed upon heating, even at 105 °C in d_8-toluene. Considering that the frequency difference between the diastereotopic signals is 28 Hz, this indicates an activation barrier larger than 80 kJ·mol^{-1}.

The saddle shape of **4** gives rise to two sizable cavities between two pairs of quinoline rings facing each other. A first evidence of the potential of **4** for binding aromatic guests in these cavities is given by the way it is packed in the crystal. Both cavities of each macrocycle are occupied by quinoline groups belonging to two other macrocycles, and by included chlorobenzene solvent molecules which fill the remaining spaces (Figure 2c). Each quinoline guest is stacked face-to-face with both quinoline rings of the host cavity. However, the cavity is slightly wider than the thickness of the guest, which lies closer to one side of the cavity. This association mode leads to the formation of discrete objects having the shape of a rosette consisting of 12 molecules of **4** clipped into one another. The rosettes are hexagonally packed in layers (Figure 2d) that are offset along the [110] direction. The hollows of the rosettes and the spaces between them are filled with the isobutyl side chains. These objects are reminiscent of the rosettes based on hydrogen bonding between melamine and cyanurates.[14] But to the best of our knowledge, they represent the first example of a rosette based solely on aromatic−aromatic interactions.

In solution in chlorinated or aromatic solvents, increasing concentrations leads to upfield shifts of the signals of aromatic protons ($\Delta\delta > 0.2$ ppm), which is consistent with some kind of aggregation. However, it is not clear from simple chemical shift variations whether these aggregates correspond or not to the rosettes observed in the solid state. ESMS measurements revealed the presence of oligomers but gave no evidence of a well-defined aggregate. Upon adding a protic solvent such as methanol to a concentrated dichloromethane solution of **4**, ^{1}H NMR first reveals upfield shifts of the signals followed by broadening and the formation of an organogel. Under the same conditions, trimer **3** precipitates instead of forming a gel.

Molecular recognition within the cavities of **4** was probed with anhydrous *p*-toluenesulfonic acid (PTSA) as a guest.[15]

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(15) This compound is not soluble in pure $CDCl_3$ and 1% of CD_3OD was added to dissolve it.

Upon titrating PTSA with **4**, upfield shifts of the guest aromatic ($\Delta\delta = 0.6$ ppm) and aliphatic ($\Delta\delta = 0.2$ ppm) ^{1}H NMR signals are observed suggesting that it is bound in the cavities of **4**.[8] Upon titrating **4** with PTSA, the amide signal shifts downfield ($\Delta\delta = 1.7$ ppm), suggesting that, in addition to π-stacking, complexation involves hydrogen bonding between the sulfonic acid function and the amide groups of **4** (Figure 3). Additionally, PTSA is expected to partially

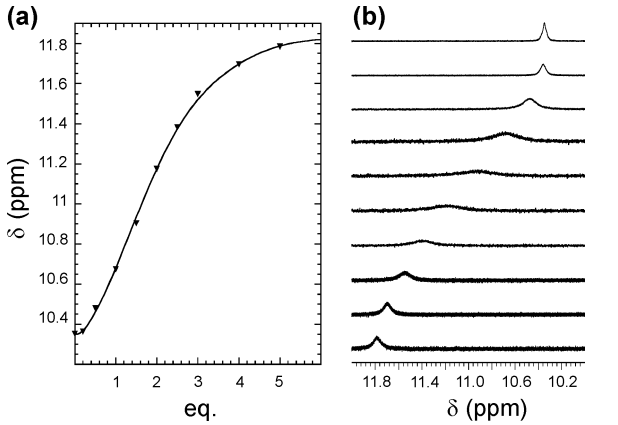

Figure 3. (a) Experimental (triangles) and calculated (line) data of the titration curve of **4** by PTSA in $CDCl_3/CD_3OD$ (99:1 v:v) at 25 °C. (b) Part of the 400 MHz ^{1}H NMR spectra (amide signal) of the titration experiment.

protonate quinoline nitrogens, especially when they are not involved in two hydrogen bonds,[16] and electrostatic interactions probably also contribute to the association.

The stoichiometry of the complex was determined by a Job plot showing that two PTSA molecules are bound by each macrocyclic host.[8] Curve fitting of the titration data allowed us to calculate the binding constant of one guest molecule $K(a_1) = 2450$ L·mol^{-1} and of two guest molecules $K(a_t) = 7\,500\,000$ L^2·mol^{-2}. The binding constant of the second PTSA molecule is thus $K(a_2) = K(a_t)/K(a_1) = 3060$ L·mol^{-1}, to be compared with $K(a_1)/4 = 610$ L·mol^{-1} that would be expected if the two binding events were equivalent. These values thus indicate a positive allosteric effect between the two binding events. Presumably, binding the first PTSA molecule induces conformational changes of the host that favor binding the second molecule.[17] This positive cooperativity is qualitatively illustrated by the sigmoidal shape of the titration curve of **4** by PTSA (Figure 3a). A quantitative analysis using a Scatchard plot allowed us to calculate a Hill coefficient of 1.38.[8]

These results illustrate the high potential of **4** for binding aromatic acid guests and forming unusual assemblies based on aromatic stacking. Its inner rim is an octaaza-24-crown-8 macrocycle similar to that of cyclopeptidic ionophores found in marine organisms,[18] and related to dibenzo 24-crown-8, a component of numerous pseudorotaxanes.[19] Metal ion binding and rotaxane formation by **4** will thus be explored in the future.

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Supporting Information Available: Crystallographic data in CIF format, synthetic procedures, and NMR titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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