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Oligocholate foldamer with 'prefolded' macrocycles for enhanced folding in solution and surfactant micelles

Xueshu Li, Yan Zhao *

Department of Chemistry, Iowa State University, Ames, IA 50011-3111, USA

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ABSTRACT

A cholate oligomer was synthesized with six linear cholate groups sandwiched by two tricholate macrocycles at the two termini. Two pyrenyl labels on the compound allowed its conformation to be studied by fluorescence spectroscopy. The linear/macrocyclic hybrid oligomer was found to fold consistently better than a linear analogue in mixed organic solvents and surfactant micelles. The enhanced folding was hypothesized to occur as the tricholate macrocycles, by their prefolded configuration, facilitate the preferential solvation of the facially amphiphilic cholate groups. In general, the folding-enhancing effect was stronger as the environment became more challenging for the oligocholate to fold. Most unusually, the hybrid oligocholate folded better in a more challenging binary methanol/ethyl acetate mixture than in the methanol/hexane/ethyl acetate ternary solvents that have been considered the most 'folding-friendly' to all other cholate foldamers.

1. Introduction

Foldamers as synthetic mimics of conformationally controlled biopolymers have attracted many chemists' attention in recent years.[1–7] In comparison to preorganized macrocycles that are the favorites of supramolecular chemists, foldamers are highly tunable due to their conformational mobility. There are several immediate benefits resulting from this tunability. First, as a linear oligomer undergoes a conformational change, its size, shape, and distribution of functional group could change accordingly, often in response to temperature, solvents, and/or the presence of other molecules and ions in the solution. For this reason, conformational control can be used as a rational way to create environmentally responsive materials including sensors,[8] 'smart' catalysts,[9] and even mechanically responsive materials.[10–12] Second, the conformational energy stored in the foldamer backbone may be used to modulate the molecular recognition of foldamer-based receptors. Whereas a macrocyclic multidentate ligand may bind a metal ion with extraordinary affinity as a result of the chelate effect, the cooperatively folded counterpart may have either very tight or very loose binding depending on the environment. This tunability is immensely useful in the controlled binding and release of guest molecules or ions.[13] Third, the cooperative conformational change of a foldamer host can be exploited to "magnify" its binding affinity for a guest that triggers additional intrahost interactions during the binding.[14] Such cooperative binding is seen frequently in bimolecular recognition including the extraordinary binding between biotin and streptavidin.[15,16]

Given the highly efficient binding, catalysis, and molecular transport displayed by biofoldamers, chemists have every reason to believe that, with increasing knowledge in the construction and utilization of conformationally controlled molecules, superior materials with protein-like functions may emerge.[1–7] Foldamer-based synthetic antimicrobial agents,[17–21] protein surface-binders and inhibitors,[22–25] vesicles and organogellators,[26] and biomimetic enantioselective catalysts[27] have all been reported in recent years. In some cases, synthetic foldamers having quaternary structural order were even synthesized.[28,29]

Our group has developed a class of foldamers from a naturally occurring facial amphiphile, cholic acid.[30–32] The oligocholates are characterized by several unusual features: (a) they fold into helical structures with nanometer-sized internal hydrophilic cavities. Cavities of this size are typically found in the tertiary and quaternary structures of proteins but are formed in our foldamers prepared in a few steps from the cholate monomer (Fig. 1); (b) their conformation is extremely sensitive to environmental stimuli. Changes in the solvent composition by a few percent have been shown to trigger complete unfolding of the folded helix, making the oligocholates particularly useful as sensors and environmentally responsive materials; (c) their synthesis is highly modular and their

* Corresponding author. Tel.: +1 515 294 5845; fax: +1 515 294 0105; e-mail address: zhaoy@iastate.edu (Y. Zhao).

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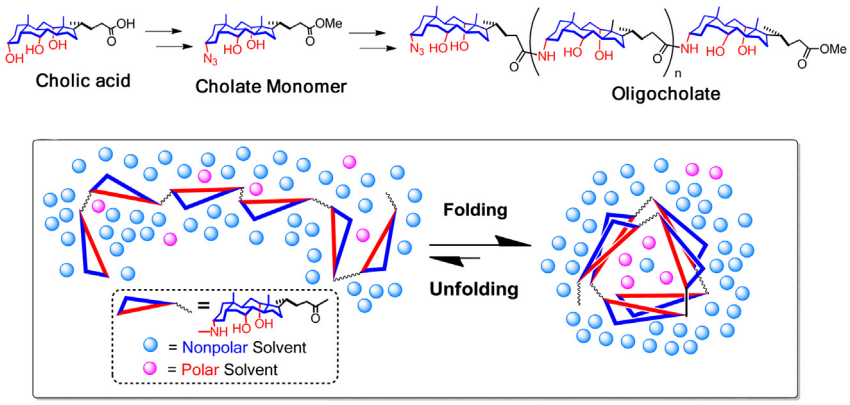

Fig. 1. Synthesis of an oligocholate and its solvophobic folding of the oligocholate.

functionalization can be achieved easily by the incorporation of natural α-amino acids; (d) their solvophobic folding has outstanding tolerance for structural perturbation[33]; (e) their conformational change is highly cooperative, similar to the two-state folding/unfolding of many proteins.[34]

Learning to control the conformation of a molecule is the most fundamental aspect of foldamer chemistry. In the past, hydrogen-bonded salt-bridges,[34] metal–ligand complexation,[13,35] aromatic donor–acceptor interactions,[36] flexible tethers,[33] and the preferential solvation of charged functionalities by polar solvent[34] have been demonstrated to enhance the solvophobic folding of the oligocholates in organic solvents. However, due to the strong environmental dependency of the folding, some of these 'folding-enhancing' methods became ineffective or even detrimental in other environments such as surfactant micelles.[34,37] In this paper, we report a new strategy to enhance the folding of the oligocholates, through incorporation of 'prefolded' cholate macrocycles in the structure. The macrocycles were shown to enhance the folding of the remaining, linear cholate groups. This effect has been shown to persist over organic solution and surfactant micelles and becomes stronger as the environment is more challenging for the folding. Most amazingly, the macrocycles enabled the hybrid foldamer to do what seemed to be impossible, i.e., to fold better in a less 'folding-friendly' solvent.

2. Results and discussion

2.1. Molecular design and syntheses

Synthesis of the linear/macrocyclic hybrid dodecamer (**1**) is shown in Scheme 1. An all-linear analogue (**2**) was prepared previously[38] and used as the control compound for the conformational study. Several considerations went into the design of the hybrid foldamer.

First, the compound consists of six linearly arranged cholates in the middle and two macrocyclic tricholate units at the ends. The driving force for the folding of the oligocholates derives from the preferential solvation of the cholate polar groups by the polar solvent molecules that phase-separate from the bulk mixture into the nanocavity (Fig. 1).[31] The size, shape, and polarity of the solvent molecules are all known to impact the folding strongly. Recently, we established that the same solvophobic driving force to help a linear oligocholate to fold could make cholate macrocycles such as **13** stack on top of one another in lipid membranes.[39] Because the folded helix of a linear oligocholate has three cholate groups per turn,[30] **13** essentially represents the cross-section of the folded helix. Since a cholate macrocycle is already fixed into the folded state by the covalent framework, having two of such units in **1** is analogous to 'prefolding' half of the dodecamer. The anticipation is that the macrocycles would concentrate the polar solvent into their interior and induce the cholate groups of the linear segment of **1** to fold.

Second, unlike the head–tail arrangement of the repeat units in typical oligocholates, symmetry is introduced in the structure of **1** to maximize synthetic efficiency. As shown in Scheme 1, the linear hexacholate in the mid-section of the molecule was obtained by coupling two identical trimer acids (i.e., the carboxylic acid derivative of **6**) to *para*-xylylenediamine, doubling the chain length of the product (**7**) in one step. Not only so, trimer **6** already had an azido group at one end of the oligomer, as a result of the azido-functionalized cholate monomer (Fig. 1). Hence, the azide–alkyne click reaction[40,41] could be employed conveniently to 'click' two alkyne-functionalized macrocycles (**12**) directly onto **7**, doubling the chain length again in another step. Note that the alkyne in **12** was introduced via the phenol side chain of a tyrosine inserted in the cholate macrocycle. In the end, the highly convergent synthesis and strategic usage of naturally functionalized α-amino acids made it possible to synthesize a complex, conformationally controlled macromolecule over 6000 Da in M.W. in just a few steps from trimer **3**.

Third, two pyrenyl labels were introduced at the two ends of hexacholate **7** via two L-ornithines. Due to its exceptionally long fluorescence lifetime, pyrene forms excimer readily at a sufficiently high concentration or if two pyrenyl groups are held together in proximity.[42] Because the trimeric periodicity of the oligocholate foldamer, pyrenyl groups at the ends of a folded hexacholate can be used to monitor the folding.[36,38]

It should be mentioned that the above synthetic designs are only possible because the solvophobic folding of the oligocholates has extraordinary tolerance for structural heterogeneity.[38] Since the folding is essentially driven by a solvent effect, there is no requirement for precise alignment of functional groups as in hydrogen-bonding interactions. In fact, flexible spacers have been shown in a previous work to facilitate the folding of oligocholates in mixed organic solvents, presumably because the folded helices have lower strain than those formed by the more rigid, parent foldamers.[33]

2.2. Folding in mixed organic solvents

The essence of the preferential solvation in Fig. 1 is the solvophobic interactions of the polar faces of the oligocholate in a largely nonpolar solvent mixture. In a nonpolar-dominant solvent, the extended conformer is disfavored because of its exposed polar faces to the nonpolar environment. By folding into a helix with introverted hydrophilic groups, the oligocholate creates a hydrophilic internal cavity filled disproportionally with the polar solvent, allowing the polar faces to largely avoid exposure to the nonpolar solvent.