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Macrocycles consisting of flexible and rigid segments: enforced folding and host-guest inclusion exciplex formation

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ABSTRACT

Macrocycles consisting of two tris(phenylene ethynylene) (or tri-PE) units connected via two flexible linkers adopt an 'unfolded' conformation that is converted into a folded conformation upon introducing intramolecular hydrogen bonding interaction. These foldable macrocycles are capable of forming inclusion charge transfer (CT) complex with electron-deficient small aromatics.

1. Introduction

Well-defined molecular and supramolecular structures are generated by restricting the relative rotational and translational motion of two or more structural components using multi-point interactions.[1] The formation of supramolecular assemblies with defined shapes relies on multi-point intermolecular interactions that act cooperatively.[2,3] Folded molecular structures of both natural[4] and unnatural[5,6] origins are examples of intramolecular self-assemblies in which the corresponding sub-structural components are connected via both covalent and non-covalent forces. The relative motion of covalently linked structural units of a folded structure leads to conformational change that plays a critical role in various binding and catalytic events. We recently described double-decked molecular crescents based on macrocycles that consist of flexible covalent tethers and two *para*-linked phenylene ethynylene (PE) halves with a persistent shape.[7] To further explore the generality of the observed folding behavior, we set out to investigate the effects of structural variations on the conformational transitions of these molecules. Macrocycles **1** (Scheme 1) with two benzene units that flank their central *meta*-linked residue were prepared.

2. Results and discussion

^{1}H NMR dilution studies in $CDCl_3$ revealed that there were no appreciable changes of chemical shifts from 1 mM to 10 mM for macrocycle **1a**, which suggested that **1a** did not engage in significant intermolecular aggregation within this concentration range. In comparison to the aromatic protons of **2a**, which can be regarded as being half of **1a**, the aromatic protons of **1a** show small upfield shifts (from 0.01 ppm to 0.11 ppm). In contrast, the aromatic protons of fully folded macrocycle consisting of two stacked halves, were found to undergo much larger upfield shifts (up to 0.23 ppm) as compared to its untethered tri-PE 'half'.[7] These results suggested that, compared to those of **1**, the two tri-PE halves of **1a** have a low propensity for stacking interaction, which implies that **1a** may adopt a conformation that is different from the fully folded ones.[7]

The crystal structure of **1a** (obtained from $CHCl_3/CH_3OH$ by slow evaporation of solvent) (Fig. 1) reveals that the two halves of **1a** only partially overlap, with the disulfide-tethered benzene residues sitting on top of the ethynyl moieties, leading to a 'partially folded' conformation in which the concave edges of the two tri-PE units roughly face each other and the two *meta*-linked benzene rings

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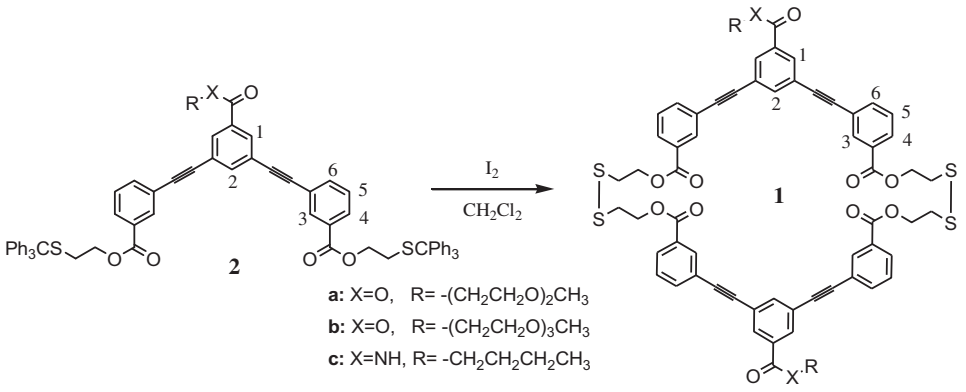

Scheme 1. Synthesis and structures of macrocycles **1**.

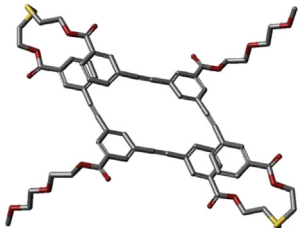

Fig. 1. The solid-state structure of macrocycle **1a**. Hydrogen atoms are omitted for clarity.

were apart from each other by pointing to nearly opposite directions. The crystal structure of **1a** has provided an explanation on why the observed upfield shifts of the aromatic protons of **1a** were smaller than expected. The crystal structure also suggests that a subtle structural change, i.e., from *para*- to *meta*-substitution, leads to dramatic changes in folding behavior.

It was expected that, if additional forces were introduced via structural modification, the conformation of the resultant derivative may be tuned accordingly. To probe whether enhancing the strength and directionality of non-covalent interaction between the two tri-PE halves could enforce a folded conformation, the ester groups of **1a** or **1b** were replaced with a secondary amide group to give macrocycle **1c**. With its two amide side chains capable of forming an intramolecular H-bond, macrocycle **1c** may adopt a folded conformation similar to those observed for fully folded ones. Examining **1c** with ^{1}H NMR revealed that, in contrast to the small shifts exhibited by the aromatic protons of **1b**, those of macrocycle **1c** showed noticeable upfield shifts (up to 0.21 ppm) relative to the protons of **2c** (see Supplementary data). Besides, the amide proton signal of **1c** showed a large (0.90 to ~1.00 ppm) downfield shift relative to that of **2c**. The observed downfield shift of the amide proton of **1c** was essentially independent of concentrations (from 2 mM to 8 mM, see Supplementary data), which demonstrates the presence of intramolecular H-bonds and suggests that intermolecular aggregation is negligible. The ^{1}H NMR data of **1c** confirmed our expectation that, due to the presence of an intramolecular H-bond between its two amide groups, compound **1c** adopts a folded conformation reminiscent of those fully folded ones.[7] Meanwhile, data from the NOE difference spectra of **1c** in deuterated chloroform also confirmed that compound **1c** adopts a folded conformation (Fig. 2).

When the signal of C1−H was saturated by irradiation, it is apparent that the signals of C2−H and CONH show NOE noticeable changes. Two peaks, one upward and the other downward, are observed for C2−H. This observation may be explained by the presence of two different C2−Hs caused by the folding of **1c**, which leads to two different distances and thus different NOE contacts between C2−Hs and C1−Hs. Specifically, due to the folding of **1c**, the one C2−H that shares on the same benzene ring with C1−H, is different distance-wise from the other C2−H that is on the other benzene ring. However, both C2−Hs are close to C1−H as indicated by the observed NOEs. This result supports the folded conformation of **1c**.

Similar phenomenon was observed when C1′−H was saturated. The signal of CONH now splits into a doublet. It is likely that the doublet indicates that the two of CONH protons, one from the CONH on the same side chain and the other from the side chain on the other half of the molecule, are all placed into close proximity to the C1′−H. This also supports the folding of **1c**.

Intrinsic fluorescence has been widely applied to study the conformational states and transitions of protein[8] and synthetic foldamers such as oligo(phenylene ethynylenes) in solution.[9] Fig. 3a summarizes the absorption and emission spectra of **1b**, **1c** (3.0 μM, excitation 285 nm), and **H1c** (6.0 μM, excitation 285 nm) measured in methanol. **H1c** can be regarded as half of **1c**. The absorption and emission spectra of the three compounds are very similar. The absorption peaks of **1b** are at 285 and 302 nm, **1c** at 284 and 304 nm, and **H1c** at 280 and 303 nm, respectively. The emission maximum of **1b**, **1c**, and **H1c** is at 365 nm, 355 nm, and 355 nm, respectively. These results are not surprising since all three structures share the same chromophore. Apparently, the nature of side chains (ester or amide) does not have any effect on the photophysical characteristics of these molecules. However, the emission intensity of **1c** is significantly lower than those of the other two compounds (**1b** and **H1c**), with the order of maximum intensity of both absorbance and emission being **H1c**>**1b**>**1c**. Furthermore, no significant difference was observed in the excited state dynamics of **1b** and **H1c**. Both display a similar fluorescence lifetime of 4.1 ns (Fig. 3b and Supplementary data). However, the excited state of **1c** shows an increased lifetime of 5.1 ns, which strongly suggests the existence of intramolecular interactions between the two PE halves of **1c**. Taken together, the fluorescence decrease observed for **1c** is most likely due to quenching caused by its folded conformation in which the two tri-PE units are brought into close proximity, most likely in a superposed fashion. It is apparent that the observed strong fluorescence of **1b** and **H1c** also arises from their conformations in solution. Significant interaction between two tri-PE units of **1b** like that of **1a** is not likely because of its partially folded conformation. Compound **H1c**, being molecularly dissolved in solution, should not engage in any meaningful intermolecular aggregation. The nearly identical emission intensities of **1b** and **H1c**, which are much stronger than that of **1c**, provide experimental