行政院國家科學委員會專題研究計畫　期中進度報告

超分子協同行為研究(2/3)

計畫類別：個別型計畫
計畫編號：NSC93-2113-M-002-008-
執行期間：93 年 08 月 01 日至 94 年 07 月 31 日
執行單位：國立臺灣大學化學系暨研究所

計畫主持人：梁文傑

報告類型：精簡報告
報告附件：出席國際會議研究心得報告及發表論文
處理方式：本計畫可公開查詢

中　華　民　國 94 年 5 月 13 日

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Novel proton-induced foldamer based on pyridine-cyclicurea oligomers

Foldamers[1] have fascinated chemists for decades due to their different biomolecular functions and optical behaviors between their conformationally disordered states into a conformationally ordered state. The foldamers system in literature have been mainly organized into four major categories: peptidomimetics, single-stranded abiotics, nucleotidomimetics, and multistranded abiotics. In this proposal, we are interested in designing a self-organized proton channel that could be activated in the presence of protons. Herein we reported a single-stranded abiotics system by protonation on pyridine-cyclicurea oligomers to examine folding process.

Hydrogen bond is widely-fabricated non-covalent interaction of supramolecule, the determination of persistent structural motifs has allowed their integration into the design of programmed molecular components for self-assembly. Urea is electron density abundant to be a good hydrogen donor. In our previous research the (*Z*,*Z*) form of pyrid-2-yl urea would transform to the (*E*,*Z*) form by a competitive intramolecular hydrogen bond between the pyridyl nitrogen and the ureido hydrogen, so we choose the cyclicurea as candidate to prevent from the intramolecular hydrogen bonding between the free urea and pyridinium. During last year, we successfully synthesis the pyridine-cyclicurea oligomers **(1)**, **(2)**, and **(3a, 3b)** and theit foldamer properties in the protonation process have been investigated.

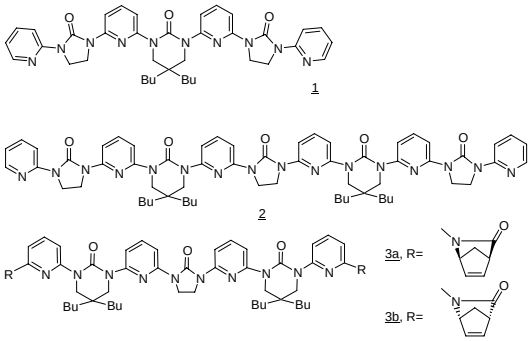


Figure 1. oligomers (1), (2), and (3a, 3b)

Neutral oligomer **(1)** adopts a linear conformation in the x-ray analysis. When triflic acid was added, protonation on the pyridino-moiety was evidenced. The pyridinium rings of the oligomers were flipped over to form hydrogen bond with the oxygen of cyclic urea, so that the oligomer **(1)** would be transformed from the unfolded conformation into a folded conformation. According to the results of ^{1}H NMR analysis, protonation occurred first at the outside pyridines during titration. This observation indicated that the outer pyridines are more basic than the inside pyridines. The stepwise protonation mechanisms were further supported by CD titration and 2-D NMR analyses.

To evidence the proton-induced folding process, NMR titration experiments for oligomer **(1)** with triflic acid were carried out. Based on the NOESY signals, we can concluded three sets of NOESY correlations (H4, H8), (H5, H9), and (H7, H10) when CF_3SO_3H (4 equiv) is added in CH_3CN solution. (plot 1). The results clearly demonstrated that oligomer(**1**) could be transformed from unfolded structure to folded structure through protonation **(**figure 2**)**.

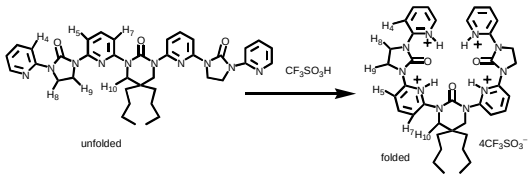
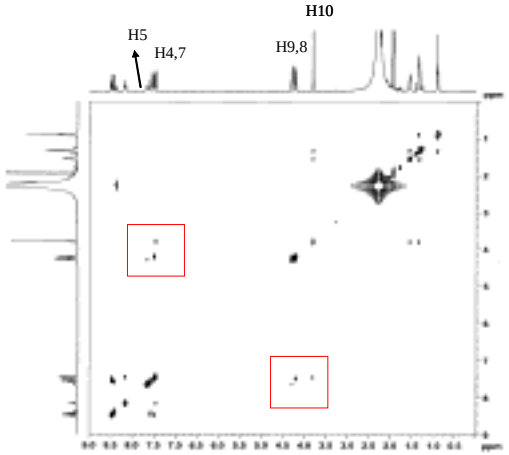


Figure 2. oligomer **(1)** unfolded structure convert to folded structure.



Plot 1.NOESY plot of oligomer **(1)** (2.42 mM) with 4 equiv CF_3SO_3H in CD_3CN.

Stepwise protonation was also evidenced in the titration plot (Figure 3). Chemical shifts of H4, H6, H5 and H7 in the titration plot showed stepwise change in the regions of 0-2 equiv and 2-4 equiv of CF_3SO_3H. When the amount of CF_3SO_3H is over four equivalents, their NMR chemical shifts reached to a limit and became nearly unchanged. We attributed this to the full protonation of the oligomer **(1) (**figure 3**)**.

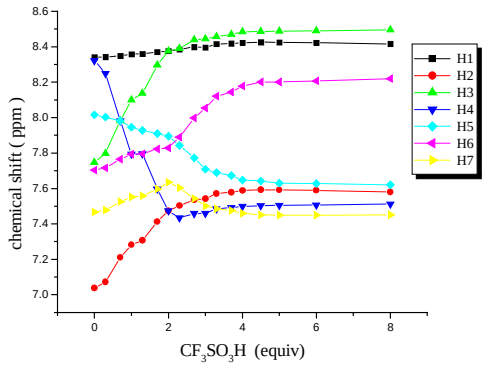


Figure 3. NMR protonation titration of oligomer **(1)** 2.42 mM with CF_3SO_3H in CD_3CN at 25 ^{o}C.

Oligomer **(2)** showed similar results in the NOESY experiment (plot 2) during which triflic acid was used as a titrant upto 12 equivalent in CH_3CN. Five sets of correlation (H4, H11), (H5, H12), (H7, H13), (H8, H14), and (H10, H15) were observed in the folded structure (figure 4).

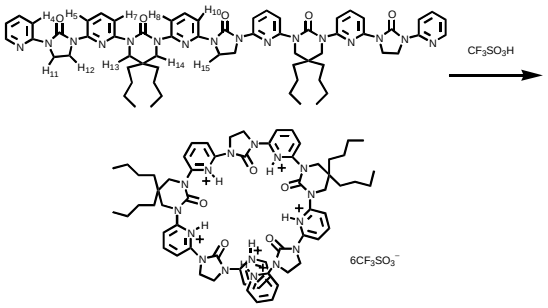
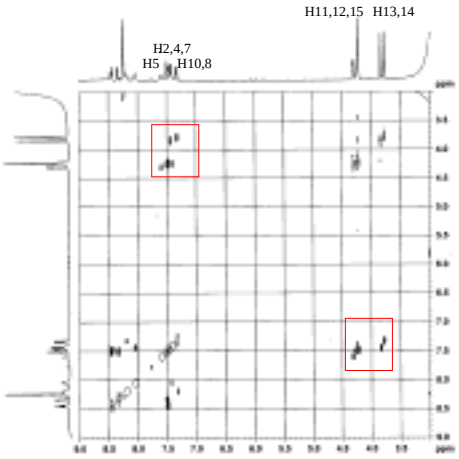


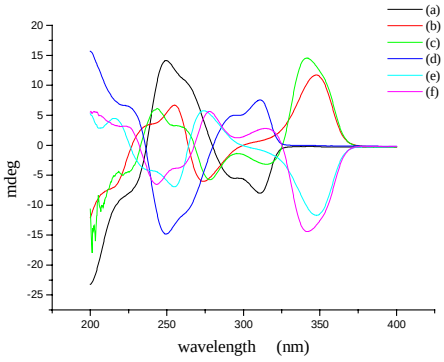
Figure 4. oligomer **(2)** unfolded structure convert to folded structure

Plot 2. NOESY plot of oligomer **(2)** 1.10 mM with 12



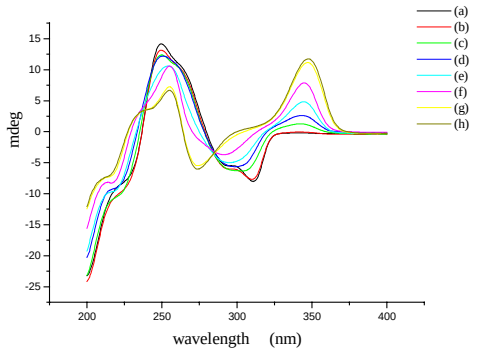
eq CF_3SO_3H in CD_3CN

The proton-induced folding process can be monitored by using circular dichroism (CD). We design the oligomers **(3a, 3b)** end-capped with chiral groups. In the CD spectra **(plot 3)**, two different conformational states can be observed respectively for of **3a** and **3b**. At the beginning of the titration, oligomer **(3a)** displayed a negative cotton effect, two distinct spectral transition bands with shoulder (311 nm, 249 nm) biased chiral oligomer **(3a)** can be observed in CH_3CN. When triflic acid was added, new broad bands at 342 nm and 348 nm appeared. These bands are assigned to the absorption of the pyridinium groups. At the lower dosage of triflic acid, the band at 348 nm first occurred alone. We tentatively assign this band to the absorption of the outer pyridinium signals. When the dosage of triflic acid increased, a pair of negative cotton CD signal peaked at 320 and 342 nm with the turning point at 330 nm. We assigned this band to the absorption of the inner pyridinium rings. More interesting is the fact that the negative Cotton CD pattern suggested that the chirality of the terminal groups were transferred to the central part after protonation. This observation implied the helix formation.

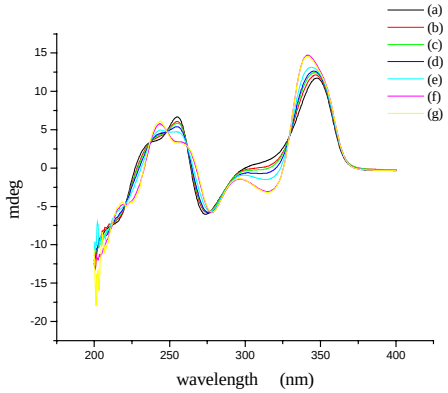


Plot 3. CD spectra.(a) 3a (8.36 μ M), (b) 3a (8.36 μ M) with CF_3SO_3H (1.02 mM), (c) 3a (8.36 μ M) with CF_3SO_3H (30.6 mM), (d) 3b (8.36 μ M), (e) 3b (8.36 μ M) with CF_3SO_3H (1.02 mM), (f) 3b (8.36 μ M) with CF_3SO_3H (30.6 mM) in CH_3CN at 18 °C.

In conclusion, pyridine-cyclicurea oligomers were synthesized, and their folded protonated structure were evidenced by 2-D NMR experiments and CD experiments.



Plot 4. CD spectra of 1st protonation step of 3a.(a) - (h) 3a (8.36 μ M),with CF_3SO_3H (0, 51 μ M, 61.2 μ M, 81.6 μ M, 91.8 μ M, 102 μ M, 204 μ M and 1.02 mM in CH_3CN at 18 °C



Plot 5. CD spectra of 2nd protonation step of 3a. (a)-(g) 3a (8.36 μ M) with CF_3SO_3H (1.02 mM, 4.08 mM, 6.12 mM, 7.14 mM, 10.2 mM, 20.4 mM and 30.6 mM.

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(1)(a) D. J. Hill, M. J. Mio, R.B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev*. **2001**, *101*, 3893-4011; (b) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173-180.