

The crystal structure, self-assembly, DNA-binding and cleavage studies of the [2]pseudorotaxane composed of cucurbit[6]uril

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Received 10 September 2006; revised 14 November 2006; accepted 16 November 2006

Available online 19 November 2006

Abstract—The [2]pseudorotaxanes of cucurbit[6]uril with guest molecule 1,6-bis(imidazol-1-yl)hexane (BIMH) were synthesized and characterized by ESI-MS spectrometry, ^1H NMR spectra, and X-ray diffraction crystallography. The influence of different anions on self-assembly in solid-state was discussed by X-ray diffraction crystallography. However, more interestingly, and to our amazement, we discovered the CB[6]/BIMH [2]pseudorotaxane exhibiting efficient cleavage of pBR322 DNA in physiological environment. The cleavage mechanism were studied by fluorescence spectra and the hydrolysis of bis(2,4-dinitrophenyl)-phosphate (BDNPP). From DNA-binding mode being electrostatic force and the first-order kinetics equation, we prove indirectly that the mechanism may be hydrolytic cleavage.

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Cucurbit[n]urils ($n = 4\text{--}12$) family, abbreviated as CB[n] or Q[n], have attracted more and more attention in recent years.¹ As an incontrovertible delegate of the family, cucurbit[6]uril² has been well known and widely studied in various aspects including pseudorotaxane,³ rotaxane^{3a,c,4}, and polyrotaxane,⁵ molecular necklaces,⁶ molecular switch,⁷ gene transfection,⁸ etc. In these works published, the guest molecules including mostly alkylammonium ions,^{2d,e,3b,c} pyridylmethyl-ended alkylammonium ions^{5f,g,6}, and other organic ammonium ions^{1c} were reported. No guest molecule containing imidazole group is reported. It is well-known that imidazole is the important biological activity molecule and functional group. And the imidazole residue of histidine as the active sites of enzymes and proteins is well recognized.⁹ Considering these, we have synthesized the new guest molecule, 1,6-bis(imidazole-1-yl)hexane (BIMH), and have reported the crystal structure and self-assembly of [2]pseudorotaxane composed of CB[6] and 1,6-bis(imidazole-1-yl)hexane dihydrobromide (BIMH-Br) as a short communication.¹⁰ In this study, to investigate the influence of the anions on the self-assembly, which is important as well as metal-coordinated to direct self-

assembly,¹¹ we changed the different anions and got the two crystal structures with chloride (Cl^-), and trifluoroacetate (CF_3COO^-), respectively. Although phosphate diester is far more kinetically stable than other common biological functional groups such as amides or esters,¹² the backbones of nucleic acids are elegantly hydrolyzed by nucleases to facilitate their synthesis, manipulation, and repair. Due to potentials in human medicine and molecular biology, the development of effective chemical nucleases has attracted much attention.¹³ Hydrolytic cleavage of DNA by small molecule is far more challenging. Most examples are metal ions or their complexes, involving transition metal ions¹⁴ and their complexes,¹⁵ lanthanide ions and their complexes,¹⁶ as well as actinides. However, in the above systems as chemical nucleases sometimes exists limitation in special condition.¹⁷ So people suggested a novel strategy to design and use non-metallic DNA artificial nuclease. Most recently, Kim's and Nakamura's groups have published the outcome that the CB[6] could affect the activity of spermine on DNA.¹⁸ Therefore, we wonder whether the complex CB[6]/BIMH can exhibit the similar property of hydrolyzing pBR322 DNA. The experiment outcome is positive, the experiments show that the complex CB[6]/BIMH can cleave circular plasmid pBR322 DNA at pH 7.2 and 37 °C. Furthermore, the cleavage mechanism was deduced by available methods including fluorescence spectra and the hydrolysis of bis(2,4-dinitrophenyl)-phosphate (BDNPP).

Keywords: Cucurbituril; Self-assembly; DNA-cleavage; Pseudorotaxane.

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We have reported a similar crystal structure (CB[6]/BIMH–Br) and its self-assembly,¹⁰ where the formation of superstructure was named as a pseudopolyrotaxane.¹⁹ To explore the influence of the different anions on the self-assembly, we gained another two crystals by changing different anions (Cl^- : CCDC 601457 and CF_3COO^- : CCDC 601456).²⁰ The structures and self-assembly of them are shown in Figures 1 and 2, respectively. Figure 1 gives the representative crystal structure. The hexane chain moieties are located fully inside the cavity and the protonated imidazole rings resided outside the portal.

As shown in Figure 2, the self-assembly of [2]pseudorotaxane with Cl^- anion is consistent with the one we reported.¹⁰ The highly ordered linear pseudopolyrotaxane formation was aggregated by intermolecular $\pi \cdots \pi$ (face-to-face) stacking between neighboring imidazole rings with a centroid–centroid 3.961 Å (0.0°), interpseudorotaxane C–H \cdots O and $\text{N}^+ \cdots \text{O}$ hydrogen bond interactions (Table S1). The separation between neighboring CB[6] molecules is 12.578 Å (*c* axis)

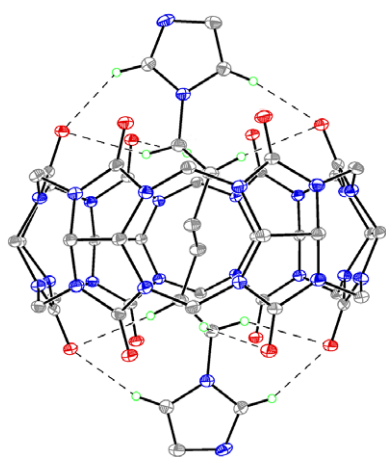


Figure 1. The represented crystal structure of CB[6]/BIMH [2]pseudorotaxanes. C atoms, gray; N atoms, light blue; O atoms, red. Side view of the structure, all H atoms, except for H atoms involved in hydrogen bonding. The minor disorder, anions, and solvent (H_2O) are omitted for clarity. Only atoms involving hydrogen bonds are labeled.

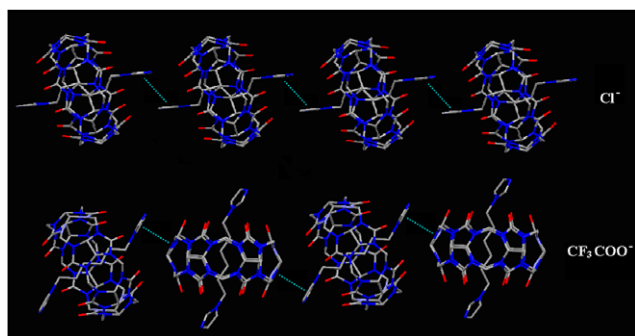


Figure 2. The self-assembly of [2]pseudorotaxane was effected by different anions. Top (Cl^-): the linear superstructure formation, may be named pseudopolyrotaxane; bottom (CF_3COO^-): zig-zag chain formation.

along $\pi \cdots \pi$ orient. However, the self-assembly of CB[6]/BIMH– CF_3COO^- complex exhibited the zig-zag chain formation due to CF_3COO^- anions' influence. The superstructure formation is mainly oriented via the other $\pi \cdots \pi$ between the guest imidazole rings from one [2]pseudorotaxane and the semi-glycoluril-ring of the host CB[6] from the other [2]pseudorotaxane with a centroid–centroid 3.454 Å (0.7°). The packings of the two crystals are shown in Figures 1S and 2S (ESI). In addition, it is made out that the packing of [2]pseudorotaxane with halide anions was more close than the one of [2]pseudorotaxane with CF_3COO^- , which was reflected in lattice density (1.747 for Br^- ¹⁰ and 1.659 for Cl^- versus 1.629 for CF_3COO^-).

The ^1H NMR spectrum (D_2O , 25 °C, TMSP as an interior criterion) characterized the structure of the 1:1 complex by only one set of signals (ESI, Fig. 3S). The signals of the methylene protons located inside CB[6] shifted upfield to (δ 3.99, 1.18, 0.57) from their original resonances (δ 4.23, 1.89, 1.33, respectively). The outside protons (for hydrogen atoms on imidazole group H1, H2, H3), the changes in chemical shifts are different. For H1 and H2, the resonances were downfield (to δ 9.16, 7.92) from their original positions (δ 8.71, 7.50) due to the deshielding effect of the portal carbonyl groups. The signal of H3, however, showed a slightly upshift field from original 7.46 to 7.37. The smaller upshift ($\Delta\delta = -0.09$ ppm) change, though the shielding region was reported by Mock being about 6 Å or 4.5 methylene groups,^{2d} should be also a result of shielding region of CB[6] due to less volume imidazole group relative to the portal of CB[6].^{3f}

An attempt of studying the superstructure assembly formation (pseudopolyrotaxane) in solution of the [2]pseudorotaxane was not successful by electrospray ionization mass (ESI-MS), which is a quite soft ionization progress that can reflect the state of molecules in solution.²¹ Though Osaka reported that the technique only detected the doubly charged CB[6] or CB[7] complex,²² our result (Fig. 4S) shows that not only doubly charged ions (m/z 608.7, $\text{CB}[6] + \text{BIMH} + 2\text{H}^+$) but also singly charged ions (m/z 1215.4, $\text{CB}[6] + \text{BIMH} + \text{H}^+$; about a half intensity) were detected. These indicate that the new CB[6]/BIMH [2]pseudorotaxane can exist stably in gas-phase as a doubly charged complex and singly charged complex.

The cleavage reaction on plasmid DNA was monitored by agarose gel electrophoresis. When circular plasmid DNA is subject to electrophoresis, relatively fast migration will be observed for the intact supercoil form (*S*, CCC form). If scission occurs on one strand (nicking), the supercoil will relax to generate a slower-moving open circular form (*C*, OC form). If both strands are cleaved, a linear form (*L*) that migrates between Form *C* and Form *S* will be generated.²³ Figure 3 (left) shows the results of cleaving superhelical pBR322 DNA in the presence of varying concentrations of the CB[6]/BIMH complex. The results indicate that the *S* form of pBR322 DNA diminishes gradually, whereas the *C* form increases with the increase of concentration of the

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