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Construction the switch binding pattern of cyclofructan 6

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ABSTRACT

A binding pattern of cyclofructan 6 and *p*-aminobenzoic acid was disclosed using electrospray ionization mass spectrometry and nuclear magnetic resonance spectroscopy. The complex with stoichiometric composition 1:1 was formed as a result of intermolecular hydrogen bond interaction and ion dipole interaction. Spectrophotometic studies demonstrated that their binding properties could be actuated by modulating the pH from 2.0 to 10.0. This is the first demonstration of development of 'switching' binding pattern for cyclofructan 6.

1. Introduction

Biomolecules such as proteins and nucleic acids can alter themselves in various levels in response to exogenous changes of environment. These phenomena inspire scientists to design and synthesize functional molecular assemblies, which could be controlled with external stimuli such as a chemical reaction,[1,2] temperature,[3,4] pH[5,6] and irradiation.[7–9] Among these external stimuli, the pH controllable systems have interesting features and state-of-the-art applications including: (1) simultaneous binding of cations and anions; (2) ON-OFF switchable sensing; (3) conformational changes within individual molecules and (4) folding/unfolding of biomolecules.[10–13] Oligomers and polymers have received considerable attention in this field.[14–16] For instance, Tanaka et al.[17] established a chiral supramolecular complexation system between amylase and oligosilane, which can be reversibly controlled by changing the pH. He and Isaacs et al.[18,19] had also reported pH switchable systems based on cyclodextrins and crown ether.

Cyclofruntan (CFs), a relatively uncultivated branch of macrocyclic oligosaccharides, have been used sparingly in a few applications such as drink bitterness attenuation, astringency, ink formulation agents and chiral selectors. They were also described as drug delivery system, which could enhance the permeability of drugs through tissue, especially in ocular and mucus tissue.[20,21] Unlike cyclodextrins, studies have demonstrated that CFs have considerable internal hydrogen bond interactions and do not possess hydrophobic cavities. Instead, their central cores have the same structure with the respective crown ethers. The physical and chemical analysis of CFs indicates that the 'cavity' increases significantly from CF6 to CF8, while their inner diameter height stays almost the same.[22–24] CFs exist in a disk-like shape with two dramatically different sides in terms of electrostatic potential: the electronegative side is composed by hydroxyl groups in the 3- and 4-positions of the fructofuranose units. The electropositive side is aligned with 1- and 6-methylene moieties of fructofuranose units.[25] Uchiyama et al.[26,27] indicated that permethylated CFs could bind barium cation with a pocket generated mainly by 3- and 4-OMe. Armstrong et al.[28,29] reported that 3-position oxygen of CFs were the most likely interaction points for the alkali metals and the buffer pH can affect the separation resolution due to the different charge state of analytes. Here two questions arise: (I) Are the host-guest interactions of CFs and guests affected by adjusting the pH condition? (II) If so, what is the binding behavior? Considering the influence of biological liquid environment in the living organism, the pH factor should be taken into account. Therefore, herein we report an interesting pH-driven host-guest interaction system based on CF6 and *p*-aminobenzoic acid (PABA) complexes. The transformation processes have been observed both in the liquid phase by one dimensional hydrogen nuclear magnetic spectra (^{1}H NMR) and two dimensional nuclear overhauser effect spectroscopy (2D NOESY) and in the gas phase using elelctrospray ionization mass spectrometry (ESI-MS).

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2. Result and discussion

Structures of the compounds used in this study are shown in Fig. 1. Amine, ketone, ester, amide and acid were all screened. Complexes of CF6-amines, CF6-amino acids and CF6-acids could be observed respectively using ESI-MS in positive mode. *P*-amino benzoic acid (PABA), which plays an important role in cell growth, was chosen as the guest model for further research due to two reasons: the aromatic ring is easily distinguished in NMR spectrum when PABA is mixed with CF6 and the zwitterionic character makes it sensitive to pH and solvent composition.

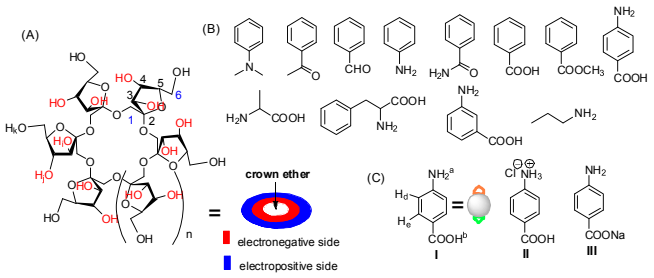

Fig. 1. Compounds investigated in this study (CFs n=6 and guests).

2.1. UV spectral study

Initial proof of principle for the pH driven binding behavior of CF6 and PABA focused on their optical properties. In a typical experiment, a mixture of CF6 and PABA in an aqueous medium adjusted to an appropriate pH value was dispersed ultrasonically. Fig. 2A showed the UV behavior of the resulting aqueous solution at different pH values for both the CF6-PABA complex and PABA (pKa_1=2.42 and pKa_2=4.90[30]). The result reflected the preferential interaction of PABA within CF6. As can be seen from Fig. 2A, the maximum absorption wavelength (λ_{max}) of PABA was red-shifted from 284 to 271 nm in acid (pH <3) due to the formation of hydrogen bond interaction and blue-shifted from 276 to 265 nm in solution with pH >6. While the absorption spectra of CF6-PABA complex and PABA guest at pH 3–5 exhibited similar spectrometric behavior. Variation in the ionization state of PABA leads to the significant changes. In pH 3–5, PABA kept as neutral molecule[31] (Guest I), which showed low affinity towards CF6. While the ionized PABA (pH <3 and pH >6) preferred to bind with CF6. pH changes may drive the binding behaviors between CF6 and PABA.

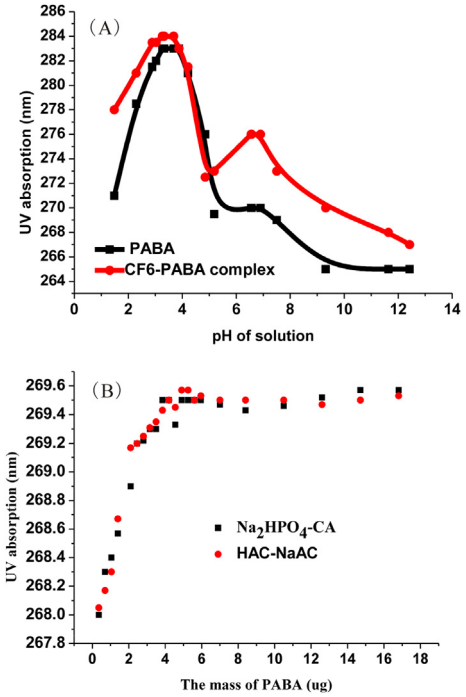

Fig. 2. (A) The UV pH-titration curves for PABA and CF6-PABA complex in aqueous solution. (B) Changes of the λ_{max} of CF6-PABA complex in different buffer solution at pH 5.0. CA is citric acid.

According to the different absorption behavior of CF6-PABA complex in acid (λ=278–284 nm, Guest II, pH 1.5–3.0) and basic solvent (λ=276–264 nm, Guest III, pH 5.5–12.0), it's proposed that the abrupt changes in λ_{max} was associated with pH dependent binding sites. To exclude the influence of ionic strength of the buffer, different buffer solutions were used at the same pH. The ionic strength of the medium was increased from 0.14 M (HAc-NaAc) to 0.26 M (Na_2HPO_4-CA). Fig. 2B compares the UV behavior of CF6 and PABA mixtures with different concentration. It can be easily observed from the titration curve that there is not a relationship between the ionic strength and the binding behavior. The trends for the complex in two buffer solutions are similar. To verify such pH driven interactions, solutions of pH 2.0, 4.0 and 8.0 were chosen for further investigation.

2.2. ESI-MS analysis

ESI-MS has demonstrated as a sensitive probe of host-guest complex ions. It allows the estimation of interaction mechanism in the absence of solvent effects. Fig. 3 showed the mass spectra of the resulting aqueous solutions containing CF6-II, CF6-I and CF6-III under soft ionization conditions. The ESI-MS provided signals at m/z 1110 in pH 2.0 and 4.0 solution, they were easily assigned to $[CF6+II]^+$ and $[CF6+I+H]^+$ ions. The sodium adducts were observed at m/z 995 and the protonated CF6 were at m/z 973. In pH 8.0 solution, the presence of singly charged 1:1 complex ions of $[CF6+III+Na]^+$ was observed at m/z 1154.

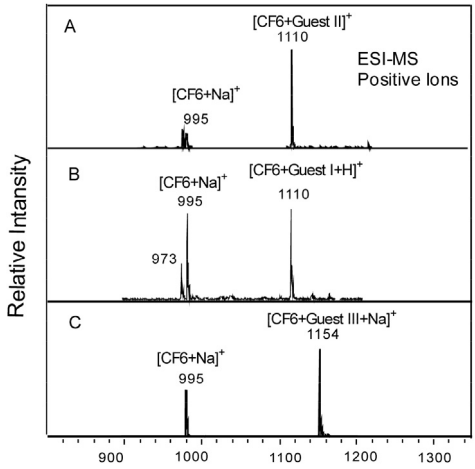

Fig. 3. Full scan mass spectra for CF6-PABA complex in solution at pH (A) 2.0, (B) 4.0 and (C) 8.0.

The complex ions of CF6 and PABA generated by ESI were isolated and subjected to collision induced dissociation. Fragmentations of m/z 1110 produced m/z 629 ion indicating the neutral loss of PABA and two fructoses units. Ions formed from direct loss of guest could not be observed even in high collision energy regime. As the internal diameter (distance between opposing oxygen atoms in crown ether skeleton) for CF6 is 2.3 Å, it's impossible to form inclusion complex with PABA. Thus, it can be conferred that PABA (form I and II) bound strongly with two fructose units of CF6 via hydrogen bond interaction and the interaction site was speculated