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Complexation of cyclofrunctans with transition metal ions studied by electrospray ionization mass spectrometry and collision-induced dissociation

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ABSTRACT

Interactions between transition metal ions (Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) and cyclofrunctans (CFs) in different solvents were investigated using positive electrospray ionization mass spectrometry (ESI-MS). ESI mass spectral analysis revealed that the 1:1 complexes were formed stably in ion trap and Fourier transform ion cyclotron resonance mass spectrometers (or in solution). The transition metal ion affinities of CFs were influenced by different solvents. In methanol and acetone, the complexation of CFs with transition metal ions was weak and the complexes of CFs with alkali metal ions were dominant. In contrast, the complexes of CFs with transition metal ions were the most abundant species in the presence of acetonitrile. The stability of inclusion complexes between cyclofructans and transition metal ions were tested by collision-induced dissociation through determining the CE_{50} values. The gas phase stability of cyclofructans in binding with transition metal cations was found to be in the order of $Ni^{2+} > Fe^{2+} > Co^{2+} > Zn^{2+} > Cu^{2+}$, which did not follow the size of ionic radius. An experimental approach based on ESI-MS is therefore established to study the host–guest interactions between cyclofructans and transition metal ions.

1. Introduction

Supramolecular chemistry has been defined as “the chemistry of the non-covalent bond” which mainly contains van der Waals, hydrophobic, electrostatic, dipolar interactions, etc. [1,2]. One important branch of the supramolecular field is macrocyclic chemistry. This includes crown ethers, cryptands, cyclodextrins, calixarenes and C_{60} among others. Of course, perhaps the most studied and useful of these entities are cyclodextrins (CDs), a group of cyclic D-glucosyl oligosaccharides that exist as either “cage” or “channel” structures [3,4]. Since it was first reported in 1891, cyclodextrins has been extensively studied in connection with many fields such as enzyme, drug, food, spice, cosmetic, agriculture, catalysis, organic synthesis, separations, chiral recognition, etc. [5–7]. The importance of molecular recognition by the formation of inclusion complexes has been recognized not only between macromolecules and small organic molecules but also between macromolecules and metal ions [8]. The first complex formed between cyclodextrin and metal cation was reported by Mstsui. Copper (II) formed a 2:1 complex with cyclodextrin in an alkaline solution by $Cu(OH^-)_2Cu$ ion bridge. [9] Later on, complexes of cyclodextrin with transition metal ions were widely studied [8]. Crown ethers are another popular host molecule which can form complexes with cations [10]. Their derivatives such as 18-crown-6-tetracarboxylic acid, benzo-crown ether and other analogs have been used for chiral recognition studies [11,12]. In particular, their ability to form stable complexes with metal ions within their central cavity via ion–dipole interaction have been extensively studied [13–15]. Recently, another unique cyclic oligosaccharide has attracted researchers’ attention. Cyclofructans (CFs) are macrocycles obtained from enzymatic conversion of inulin. They are a family of cyclic oligosaccharides composed of β-(2-1)-linked fructofuranose units [16]. Their structure is quite different from the truncated cone-shaped morphology of cyclodextrin. The crystal data shows that CF6 has an 18-crown-6 skeleton and six neighboring fructofuranose units and the fructofuranosyl moieties in inulobiosyl unit (1-O-β-D-fructofuranosyl) have almost the same conformations with the exception of their torsion angles [17]. The structure of CFs is shown in Fig. 1. There is no real cavity in CFs but it is closest in shape to an oblate spheroid. The X-ray structure shows a nonplanar molecule with extensive internal hydrogen bonding and an unexposed, twisted-deformed 18-crown-6 core [18]. The diameters of the so-called “cavity” range from 2.3 Å to 4.7 Å depending on the number of fructose constituents. [16,18] Thus the structure of cyclofructans differs substantially from those of cyclodextrins

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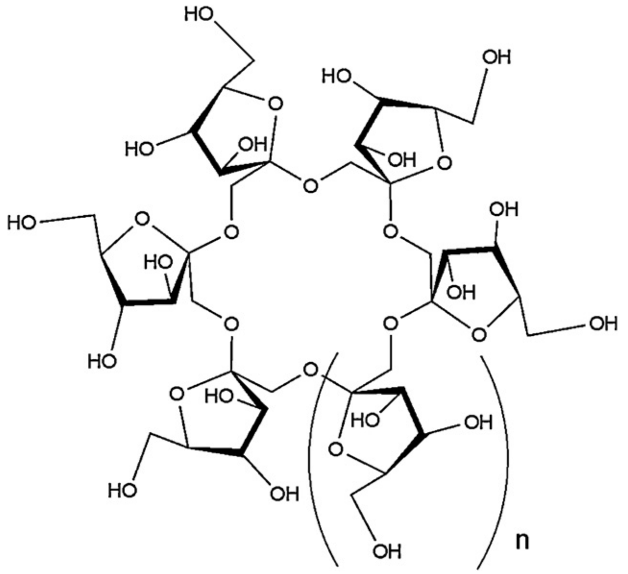

Fig. 1. Molecular structure of CFs.

and synthetic crown ethers. Recently it has been reported that cyclofructans and their derivatives are useful as stationary phases or additives for chiral discrimination in high performance liquid chromatograph, gas chromatography and capillary electrophoresis [18–21].

With the development of soft ionization techniques, especially electrospray ionization mass spectrometry (ESI-MS), the study of non-covalent complexes in liquid and gas phase has become prevalent. Host–guest complexes formed in solution can be characterized by ESI-MS, the relative abundances and the stoichiometry of the complexes formed in solution can thus be determined in the gas phase [22]. In addition to the determination of the molecular weight for complexes of macromolecules and metal ions, MS has the potential to provide structural information by using collision-induced dissociation (CID). ESI-MS has been widely used for host–guest studies of many crown ethers, cyclodextrins in solution and in the gas phase [23–25]. There are few investigations which focus on the ESI-MS study of cyclofructans with metal ions. Due to the characteristic crown ether core of cyclofructans and their vicinal hydroxyl groups, they are expected to bind cationic molecules via charge–dipole electrostatic interactions. Use of ESI-MS and the density functional theory (DFT) calculation method to study complexation between cyclofrunctans and alkali metal cations had been reported by Armstrong [26]. The gas phase stability of complexes between CF6 (or CF7) and alkali metal ions was determined to be $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, followed the order of ionic radius. The purpose of this work is to study complexes of CFs with transition metal ions using ESI-MS, to compare the binding affinity of different transition metal ions in different solvents, and to study the gas phase stability of complexes between CFs and transition metal ions by tandem mass spectrometry.

2. Experiment

2.1. Materials

All chloride salts were commercially obtained. HPLC-grade methanol, acetone and acetonitrile were obtained from Tedia company (USA). Water was purified by a Milli-Q purification system (Millipore, Bedford, MA, USA). Cyclofructans were the generous gift of AZYP, LLC, Arlington, TX. CF6, CF7 were used as received without further treatment.

2.2. Methods

All mass spectrometry experiments were carried out using a Bruker Esquire 3000^{plus} ion trap mass spectrometer (Brucker-Franzen Analytik GmbH, Bremen, Germany) equipped with an electrospray ionization (ESI) interface in positive mode. Nitrogen was used as nebulizing gas at a pressure of 10 psi and drying gas at a flow rate of 5 L min^{-1}. The drying gas temperature was set at 250 °C and the capillary voltage was set at −4000 V with a scan speed of 13,000 *m/z* units per second. Solutions containing analytes were infused to the mass spectrometer with a syringe pump at a flow rate of 6 μL min^{-1}. The collision induced dissociation experimental data for all the precursor ions were obtained with helium as the collision gas at an appropriate collision energy after isolation of the desired precursor ion. The mass window for precursor ion selection is between 6 and 8 *m/z*. Every spectrum was acquired for 0.2 min. Three spectra were averaged for each experimental data point.

Accurate masses were measured on an Apex III (7.0 Tesla) Fourier transform ion cyclotron resonance (FTICR) mass spectrometer (Bruker, Billerica, MA, USA) equipped with an ESI source in the positive ion mode. Nitrogen gas was used as the nebulizing gas and drying gas. The capillary voltage was set at (−3900) to (−4200) V, and the drying gas temperature was set at 150 °C. The solution was infused at a rate of 3 μL min^{-1}.

3. Results and discussion

The water-organic solvent (1:1, v/v) consisting of 1.1×10^{-5} M MCl_2 ($M = Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}$, and Pd^{2+}) and 5.17×10^{-6} M NaCl were prepared and then CFs (here $s = 6$ or 7) were added to a final concentration of 1.1×10^{-5} M. NaCl was used as the internal standard. The samples were then investigated by ESI mass spectrometry in positive mode. The complexes between CFs and all the studied transition metal cations, except Pd^{2+}, could be detected. The exact masses were determined by Fourier transform ion cyclotron resonance mass spectrometry and the spectra are given in the Supporting Information. According to hard and soft acid theory, crown ethers and their derivatives are hard alkalis and the oxygen atoms on the skeleton have an electron-donating effect. Thus, crown ethers generally form stable complexes with alkali metal ions, alkali earth metal ions and lanthanide metal ions. On the contrary, crown ethers do not typically coordinate with transition metal ions. However the special structure of CF6 with crown ether as the skeleton and six fructans arranging alternately, make it different in character. It has been shown that the hydroxyl oxygen atoms of CF6 are close to each other with a distance of 3.09 Å, approximately the sum of their Van der Waals radii [17]. Thus intramolecular hydrogen bonding interactions are stronger in CFs. Hydrogen-bonding can dramatically influence the magnitude of inclusion of transition metal ion complexes by acting as a ‘molecular snaps’ [27]. Meanwhile, the hydrophilic side formed by the hydroxyl groups can be considered as soft bases, so it is easier to coordinate with transition metal ions after losing a proton. One of the prerequisites for a mass spectrometric characterization of supramolecular entities is that they can be successfully charged and transferred into the gas phase without destruction. In this study, besides the complex ions of CFs with transition metal ions, no fragment ions can be detected in the full-scan mass spectra. Fig. 2 shows a representative full-scan mass spectrum for complexation of CF6 with $NiCl_2$. The characterized intense signals at *m/z* 995 correspond to $[CF6+Na]^+$ ion. The presence of the singly charged 1:1 complex of $[CF6{-}H{+}Ni]^+$ was observed at *m/z* 1029. Ions corresponding to CF6 coordinated with two metal cations were not detected. The complexation of CF6 with other transition metal ions including