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Specific and nonspecific effects of biologically active inorganic salts on inclusion complex formation of cyclodextrins with aromatic carboxylic acids

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HIGHLIGHTS

- Cyclodextrin/carboxylic acid complex formation was studied in salt solutions.
- Binding is decreased in the presence of the salts.
- Influence of Cl^- and SO_4^{2-} anions is nonspecific and insignificant.
- Anions Br^- and $H_2PO_4^-$ considerably affect inclusion complex formation.

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ABSTRACT

Inclusion complex formation of α- and β-cyclodextrins with zwitterionic nicotinic and *m*-aminobenzoic acids in water and 0.2 M solutions of KCl, KBr, KH_2PO_4 and K_2SO_4 was studied by ^1H NMR and UV-spectroscopy. We complemented the experiments with statistical mechanics calculations in the framework of the 3D-RISM approach to analyze the ion-binding between inorganic univalent anions and positively charged groups of the acids under study. It was detected that binding affinity of cyclodextrins to the acids is decreased in the presence of the salts. This is caused by specific and nonspecific action of the considered inorganic anions. The influence of the Cl^- and SO_4^{2-} was found to be nonspecific and insignificant. On the contrary, Br^- and $H_2PO_4^-$ ions can considerably affect the inclusion complex formation. Insertion of Br^- into the macrocyclic cavity and attraction between $H_2PO_4^-$ and the zwitterions are the main processes competing with cyclodextrin–acid binding. It has been demonstrated that the manifestation of the salt effects depends on the cyclodextrin cavity size, ionization state of the acid and other experimental conditions.

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1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides which are able to form inclusion (or host-guest) complexes with a wide variety of organic compounds. Owing to this property, CDs become attractive research objects and received numerous practical applications (Szejtli, 1988; Del Valle, 2004). Therefore, a detailed study of CD inclusion complexes seems to be worthwhile.

In pharmacy, CDs are mainly used as drug carriers and encapsulating materials (Szejtli, 1988; Del Valle, 2004; Ahmed et al., 2014; Zhang and Ma, 2013). Engineering of new drug delivery systems on the basis of CDs has been an active research area during the last years (Del Valle, 2004; Ahmed et al., 2014; Zhang and Ma, 2013). Therefore, the study of the inclusion complex formation of CDs with drugs and biomolecules in solutions taking into account the environment within the living organism are required to enhance the understanding of CD – drug inclusion complexes function in vivo. In particular, inorganic salts which are frequently present in cellular environments would affect the formation of CD complexes. Thus, CD complex formation in the presence of inorganic salts is of a considerable interest in developing a better understanding of the behavior of the inclusion complexes in the physiological conditions.

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The effects of KCl and KBr in complex formation of α-CD with *m*-aminobenzoic and nicotinic acids have been examined in our previous publication (Terekhova et al., 2013). Significant difference in the behavior of Cl^- and Br^- has been found. In particular, Br^- anions reduced the α-CD binding affinity towards the carboxylic acids due to their ability to penetrate into the macrocyclic cavity. On the other hand, Cl^- anions displayed a negligible influence on the α-CD–acid complexation. The observed discrepancy stimulated the continuation of our studies focused on the role of biologically active inorganic anions in CD complex formation. To this end, we have extended our investigations to a number of anions and considered the effects of $H_2PO_4^-$ and SO_4^{2-} as well as Cl^- and Br^- in complex formation of α-CD and β-CD with *m*-aminobenzoic and nicotinic acids. These anions of different nature and charge were chosen for a better understanding of salt effects in the CD inclusion complex formation. Moreover, data for β-CD complex formation in salt solutions were obtained for the first time and compared with those for α-CD binding in order to assess the influence of the CD cavity size on the manifestation of salts effects.

2. Methods

2.1. Chemicals

Nicotinic acid (NA), *m*-aminobenzoic acid (mABA), *p*-aminobenzoic acid (pABA), potassium chloride, potassium sulfate and potassium dihydrophosphate were obtained from Sigma-Aldrich. The α-CD and β-CD were purchased from Fluka. Potassium bromide was supplied by Acros Organics. All chemicals were of analytical grade and used as received. All of the solutions were freshly prepared before each experiment.

2.2. ^1H NMR

^1H NMR experiments were performed on a Bruker-AV-500 spectrometer operating at 500 MHz and temperature of 298.15 K. Deuterated water (D_2O, 99.9%) was used as solvent, and cyclohexane was applied as an external reference. ^1H NMR spectra of CD were recorded in water and salt solutions. Concentration of salt solutions was 0.2 M which is close to the concentration of Cl^- in biological fluids. We used the same concentration for KCl, KBr, KH_2PO_4 and K_2SO_4 to perform correct comparison of the salt effects. The resulting Br^-, $H_2PO_4^-$ and SO_4^{2-} concentrations, however, exceed biologically relevant concentrations.

To study complex formation, CD concentration was kept constant (0.005 mol/kg), while the concentration of NA and mABA was changed from 0 to 0.15 and 0.04 mol/kg, respectively. Stability constants of CD/NA and CD/mABA complexes in water and 0.2 M salt solutions were calculated on the basis of the concentration dependences of $\Delta\delta$ using nonlinear curve fitting procedure.

2.3. UV-spectroscopy

Absorption spectra were recorded in the range of 200–400 nm at 298.15 K on a UV-2401 PC UV–vis Recording Spectrometer (Shimadzu, Japan) equipped with TCC-240A, temperature controlled cell holder. Quartz cuvettes with a path length of 1 cm were employed. The relative error of the absorbance determination did not exceed 0.5%.

Absorption spectra of NA and mABA were obtained in pure water and CD solutions of varying concentration. Analogous measurements were performed in 0.2 M salt solutions. Concentration of NA and mABA was constant, while CD concentration was changed. Similarly to ^1H NMR, stability constants were determined from the binding isotherms by the nonlinear least-squares method.

2.4. Solubility measurements

Solubility of NA and mABA was measured in water and in salt solutions at room temperature. For this purpose, excess amounts of the solid acids required for saturation were added into sample bottles containing 10 ml of the solvent. Solutions were stirred for 2 days. Samples were taken of the supernatant liquid phase using a plastic syringe, filter through a 0.22 μm disposable filter and analyzed spectrophotometrically. Independent experiments were performed three times to avoid a systematic error.

2.5. Statistical mechanics calculations

We used the three-dimensional reference interaction site model (3D-RISM) integral equation theory to analyze the features of ion-binding between inorganic anions and the positively charged functional groups of mABA and NA. This method provides realistic information on the solution structure and on ion-binding in systems similar to those of current interest (Fedotova and Kruchinin, 2013a, 2013b, 2014).

The 3D-RISM approach described in detail (Kovalenko, 2003) operates with molecular-atom (site) spatial distribution functions (SDFs), $g_\alpha^{uv}(\mathbf{r})$, which are 3D-site (α) distribution functions of solvent (v) atoms around the solute (u) molecule. In the present case, an aqueous salt solution acts as the solvent for aromatic carboxylic acid so that the inorganic ions are regarded as solvent sites, α. The SDFs associated with ion binding were obtained from the solute–solvent 3D-RISM integral equation (Kovalenko, 2003) coupled with 3D closure (Kovalenko and Hirata, 1999a, 1999b). These SDFs were used to calculate the potential of mean force (PMF) as

$$W_\alpha^{uv}(\mathbf{r}) = -k_B T \ln g_\alpha^{uv}(\mathbf{r}) \quad (1)$$

with k_B being Boltzmann's constant and T is the Kelvin temperature. The PMF represents the ratio of the free energy of a solvent particle at a given distance from the solute with respect to the bulk. The value of the PMF between two ions at the first minimum in turn holds information on the stability of the ion pair.

Our calculations were carried out for one molecule of mABA and NA in 0.2 M KBr(aq) at ambient conditions using the *rism3d.snglpnt* from the AmberTools package (version 1.5) (Case et al., 2010). The 3D-RISM-KH equations were solved on a 3D grid of $270 \times 270 \times 240$ points with a spacing of 0.025 nm in a parallelepiped cell of size 6.75 nm × 6.75 nm × 6.00 nm. This was large enough to accommodate the complex together with sufficient solvation space around it. The numerical solution of the 3D integral equation was performed by the MDIIS (Modified Direct Inversion in the Iterative Subspace) iterative scheme (Kovalenko et al., 1999c) with 5 MDIIS vectors; a residual tolerance of 10^{-6} was chosen. Solute-atom partial charges were calculated with the *antechamber* program from the AmberTools 1.5 package (Case et al., 2010) using the AM1-BCC method (Wang et al., 2006; Jakalian et al., 2000, 2002). The corresponding LJ parameters were taken from the General Amber Force Field (GAFF) (Wang et al., 2004). The modified version of the SPC/E model (MSPC/E) was used for water (Lue and Blankschtein, 1992). Atom coordinates of the solute in water were adopted by the DFT (Density Functional Theory) at the B3LYP/6-31++G(d,p) level using the GAUSSIAN09 program package (Frisch et al., 2010).

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