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Effect of inorganic salts on the inclusion complex formation and solubilizing potency of cyclodextrins

The competition of hydrophobic molecules for the cyclodextrin (CD) cavity is well known and reported in the literature. However, it is not so trivial, how inorganic salts, small cations and anions may affect the inclusion complex formation, and thereby the functional properties of CDs. This topic is recently of particular interest for formulators since there are several granted patents and published patent applications on commercially available CD derivatives with certain intrinsic ion contents (in particular chloride and phosphate), such as US patents US7635773, US8410077, US9200088, US9493582 as well as US patent applications US2015284479 and US2015045311. All these documents highlight that the absence of these ions is specifically favored. On the other hand, the patent disclosing the SBE-BCD-based amiodarone formulation (US6869939) states that the advantage of using SBE-BCD is that a wider range of buffers was found compatible compared to other known (surfactant-containing) amiodarone-containing liquid formulations. Suitable buffering agents were enumerated such as phosphate and borate. In Example 10 of patent US6869939, a suitable formulation containing amiodarone HCl (50 mg/mL) in a solution containing 114 mM monobasic sodium phosphate and 30% w/v SBE-BCD is illustrating the advantageous use of phosphate ions in a SBE-BCD based formulation.

Effect of inorganic ions on the complexation with native CDs

In the pioneering work of Mochida et al. (1973) dealing with the effect of inorganic ions on the complex formation with CDs both positive and negative effects were described. The apparent association constant (K_{app}) of a complex between β-cyclodextrin (BCD) and an azo dye, Na p-(4-hydroxy-1-naphthylazo) benzenesulfonate (HNB) determined by spectrophotometry in a phosphate buffer solution (pH 5.91) increased or decreased in the presence of other salts (Fig. 1). While K_{app} almost doubled in the presence of potassium sulfate, it decreased to the half or less with KI, KSCN and $KClO_4$.

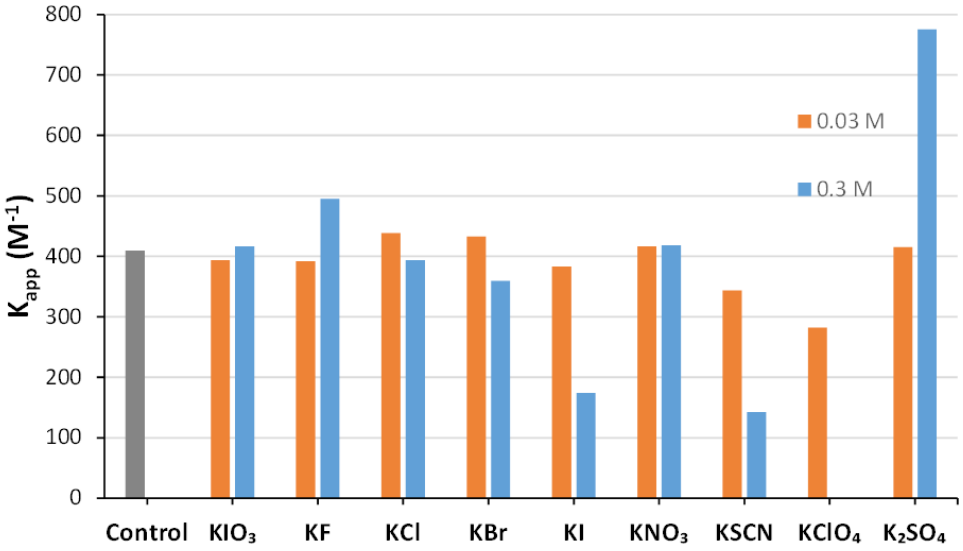

Fig. 1. The apparent association constant of Na HNB azo dye in the presence of various inorganic salts at 0.03 M and 0.3 M concentration in 0.1 M phosphate buffer (data calculated from Mochida et al. 1973)

The decrease of the association constant was attributed to competitive binding between the dye and the inorganic anion. Based on this assumption the order of anions concerning their affinity toward the CD cavity is as follows:

ClO_4^- >> SCN^- > I^- > Br^- > Cl^-

The enhancement of K_{app}, explained by the decrease of water activity, follows the order of (for the effect of PO_4^{3-} see Fig. 2):

SO_4^{2-} >> F^- > PO_4^{3-}> IO_3^-

Neither increase nor decrease of the association constant of the azo dye/BCD complex was observed with KNO_3.

This order was confirmed by polarography and NMR (Taraszewska and Wojcik 1993): PF_6^-, ClO_4^- and SCN^- were complexed to a high extent, while SO_4^{2-}, F^- and PO_4^{3-}/ $H_2PO_4^-$ showed negligible effect.

In the studies of Mochida et al. (1973) K_{app} increased slightly also with an increase in the concentration of the phosphate buffer (Fig. 2). An order of magnitude enhancement in the concentration of the salt resulted in approx. 20% increase in the association constant.

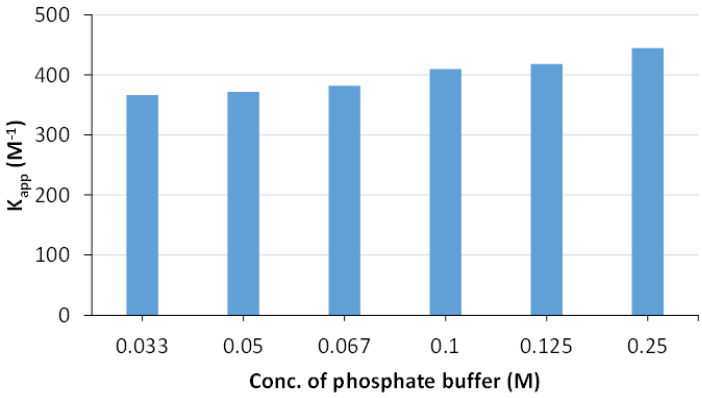

Fig. 2. The apparent association constant of Na p-(4-hydroxy-1-naphthylazo) benzenesulfonate/BCD complex as a function of the concentration of the phosphate buffer (data calculated from Mochida et al. 1973)

Buváry and Barcza (1979) studied the phenolphtalein/BCD complex in various salt solutions (Fig. 3). The apparent stability constant (β*) values were calculated by assuming the formation of mixed (phenolphtalein + anions + cations) complexes. It can be seen that certain inorganic anions play crucial role, but also the cations have a slight effect. The most stable mixed complexes are formed with sulfate and chloride ions, while thiocyanate and perchlorate rather compete for the cavity.

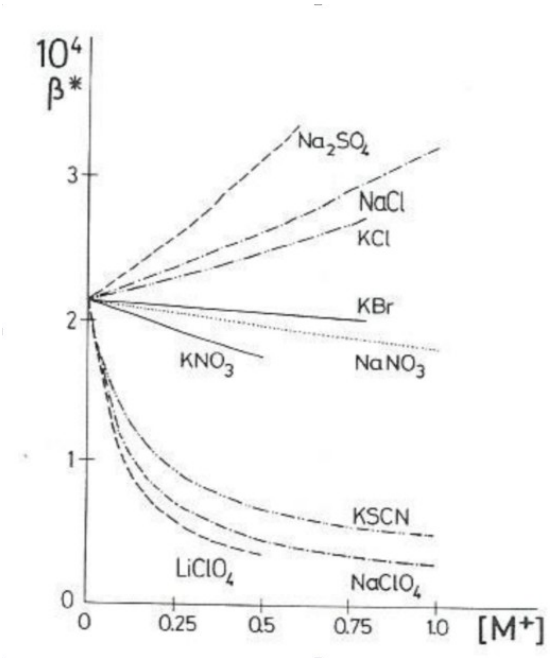

Fig. 3. Apparent association constant of mixed phenolphtalein/inorganic anion/inorganic cation complexes with BCD as a function of salts concentration (Buvari and Barcza 1979)

Similar relationships were obtained for benzoic acid and methyl orange BCD complexes (Buvari & Barcza 1989). It was concluded that the changes in water activity are of minor importance, but the formation of real inclusion complexes or the attachment of the anions from outside to the host-guest complex by electrostatic interactions or by hydrogen bonds (mixed complexes) are more conceivable.

Since the review on the complexation of inorganic ions by the native CDs in 1996 (Fenyvesi et al.) summarizing the similar findings for the three native CDs obtained by various experimental techniques including electrochemical methods, polarography and freezing point depression, only a few studies have been published.

Matsui et al. (1997) studied the complexation of inorganic anions by α-CD (ACD) using NMR. The chaotropic anions (anions disrupting the hydrogen bonding network between water molecules) such as Br^-, I^-, SCN^-, N_3^-, ClO_4^-, and NO_3^- caused marked shifts in the C(5)-H signals showing that these ions are included in the cavity of ACD. The antichaotropic anions such as F^-, HCO_3^-, $H_2PO_4^-$, HPO_4^{2-} caused no or very small shifts. Similar, but smaller effects were observed for BCD and GCD.

Yi et al. (1999) investigated some buffer components on the formation constant of 3-hydroxy-2-naphthoic acid/BCD complex using fluorescence competitive inhibition technique. The formation constants for the competing salt/BCD complexation were calculated. It was concluded that only the more lipophilic ClO_4^- and Cl^- ions were included in the cavity *via* van der Waals and hydrophobic interactions, while KF, K_2SO_4, NaH_2PO_4, Na_3PO_4, Na acetate and $NaHCO_3$ did not form inclusion complex as the formation constants were negative. These ions are located in the hydrophilic rim formed by the primary hydroxyl groups of CD.

The group of Zughul studied the effect of buffer components on complex formation of various drugs with BCD (Al Omari et al. 2006, 2006a, 2007 and 2009). Celecoxib was the model acidic drug fully ionized at high pH, while unionized at acidic pH and terfenadine the model dug of basic character ionized at acidic pH and unionized at pH 12. Increasing phosphate buffer concentration enhanced the tendency of ionized drugs (celecoxib at high pH and terfenadine at low pH) to complex with BCD as a result of a corresponding decrease in the inherent solubility (S0) of the drug ions (Al Omari et al. 2006a and 2007). On the other hand, increasing phosphate buffer concentration enhanced the complexation of neutral celecoxib by lowering S_0 (solubility without CD), and decreased the solubilization of neutral terfenadine.

Effect of inorganic ions on the complexation with CD derivatives

Similarly to the native CDs the chemical shifts of some 1H NMR signals given by mono[6-(1-pyridinio)-6-deoxy]-alpha-CD in D_2O were significantly changed by the addition of alkali salts of chaotropic anions such as Br^-, I^-, SCN^-, N_3^-, ClO_4^-, and NO_3^-. However, only small changes in the values of the chemical shifts were brought about by the addition of alkali salts of antichaotropic anions or kosmotropes such as F^-, Cl^-, SO_4^{2-}, $H_2PO_4^-$, HPO_4^{2-} (Mu et al. 1993).

It was concluded that the chaotropic anions were included within the cavity and attracted the pyridinio group of CD close to the C(6)-H.

The solubility of poorly soluble Li_2CO_3 was increased to a large extent in solutions of α-, β-, and γ-CDs and DIMEB giving A_N type solubility isotherm (Song & Bai 2009). The binding ability of both D- and L-tryptophan by the CDs was increased effectively by this salt.

Table 1 lists some so far unpublished solubility data of various drugs in aqueous solutions of sulfobutyl BCD (SBE-BCD) in the presence of Cl^- and PO_4^{3-} with sodium as counter ion. The data show that neither Cl^- nor PO_4^{3-} exhibited an effect exceeding the experimental error. To perform these experiments, a research grade SBE-BCD sample (prepared by Cyclolab for internal use) containing less than 10 mg/kg intrinsic PO_4^{3-} and a commercially available lot of Dexolve (Cyclolab's Betadex Sulfobutyl Ether Sodium), having 538 mg/kg intrinsic PO_4^{3-} and less than 0.01% intrinsic Cl^- content was used. In this systematic study on the eventual effect of the presence of chloride and phosphate ions on the solubility-enhancing potential, five model drug compounds and spiked solutions of these SBE-BCD samples were used.

Table 1. Solubility data (in 20 w% SBE-BCD (Dexolve), 30 °C. Concentration unit: mg/ml)

	Ziprasidone mesylate trihydrate	Carbamazepine	Voriconazole	Diclofenac Na	Propofol
SBE-BCD PO_4^{3-}< 10 mg/kg Cl^- < 0.01 %	30 ± 2	9.5 ± 1.0	21 ± 3	34 ± 2	11 ± 1
SBE-BCD PO_4^{3-}< 10 mg/kg Cl^- = 0.2 %	29 ± 2	9.6 ± 1.0	21 ± 3	34 ± 2	12 ± 1
SBE-BCD PO_4^{3-}= 538 mg/kg Cl^- < 0.01%	30 ± 2	10.4 ± 1.0	18 ± 3	34 ± 2	12 ± 1
SBE-BCD PO_4^{3-}= 5500 mg/kg Cl^- < 0.01%	31 ± 2	10.0 ± 1.0	18 ± 3	35 ± 2	13 ± 1

BCD-bonded silica for solid phase extraction (sample preparation for concentration of the samples before chromatographic analysis) showed reduced efficiency in sorption of various nitrophenols in the presence of various salts, such as $CaCl_2$, NaCl, KCl and Na_2SO_4. The inorganic ions might either occupy the cavity or form steric hindrance at the rim resulting in reduced sorption capacity.

Densely packed monolayers of per-2,3-methylated per-6-thiolated α-, β-, and γ-cyclodextrins on the hanging mercury drop electrode made possible to study the inclusion of inorganic ions into the monolayer by capacitance measurements (Chamberlain et al. 2000). Whereas the smaller and less well solvated anions Cl^-, NO_3^-, and ClO_4^- were included in the CD cavities of

these monolayers, the larger and more strongly solvated anions F^-, SO_4^{2-}, and $H_2PO_4^-$ were excluded. On the contrary to these findings Domi et al. (2011) published that the catalytic effect of ferrocene included in perthio-CD monolayers on gold electrode was inhibited by the presence of some anions (SO_4^{2-}, NO_3^-, HPO_4^{2-}) owing to the competitive complexation of these anions. The association of SO_4^{2-}, NO_3^-, HPO_4^{2-} to the monolayer was much stronger than that of ClO_4^-, Cl^-, and Br^- showing that the surface-bound CDs behave differently compared to solution.

Conclusions

The effects of salts on the inclusion complex formation depend on several factors:

- CD type (cavity size, substituents type and degree of substitution)
- guest type (charge, affinity to CDs)
- inorganic anions (size, chaotropic property, hydrophobic character)
- inorganic cations (charge, hydrodynamic radius).

The highest effects were seen for native BCD among CD derivatives. The chaotropic anions might interfere with the H-bonding network of the OH groups hence enhancing the solubility of BCD.

The anions might decrease the solubility of the guest molecule (salting out) enhancing its affinity for complexation.

These rules are not valid for CDs bound to surfaces, which bind inorganic anions in such a high extent that sulfate can expel ferrocene out of the cavities.

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Aggregates, Microparticles, Nanoparticles, Permeation, Dorzolamide and dexamethasone

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CDplexes, Effective charge ratio, Protein corona for targeted gene delivery, Multilamellar phases

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Sugammadex, Capillary electrophoresis screening, Carboxymethylated and sulfobutylated gamma-cyclodextrin derivatives, Neurological agents, Animal study

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Hemagglutinin, Multivalent effect, Disrupting influenza HA protein-host receptor protein interaction

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HPBCD, Lipid implants, Protein stability, Ranibizumab, Monoclonal antibody

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