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The formation of host–guest complexes between surfactants and cyclodextrins

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ABSTRACT

Cyclodextrins are able to act as host molecules in supramolecular chemistry with applications ranging from pharmaceutics to detergency. Among guest molecules surfactants play an important role with both fundamental and practical applications. The formation of cyclodextrin/surfactant host–guest compounds leads to an increase in the critical micelle concentration and in the solubility of surfactants. The possibility of changing the balance between several intermolecular forces, and thus allowing the study of, e.g., dehydration and steric hindrance effects upon association, makes surfactants ideal guest molecules for fundamental studies. Therefore, these systems allow for obtaining a deep insight into the host–guest association mechanism. In this paper, we review the influence on the thermodynamic properties of *CD*–surfactant association by highlighting the effect of different surfactant architectures (single tail, double-tailed, gemini and bolaform), with special emphasis on cationic surfactants. This is complemented with an assessment of the most common analytical techniques used to follow the association process. The applied methods for computation of the association stoichiometry and stability constants are also reviewed and discussed; this is an important point since there are significant discrepancies and scattered data for similar systems in the literature.

In general, the surfactant–cyclodextrin association is treated without reference to the kinetics of the process. However, there are several examples where the kinetics of the process can be investigated, in particular those where volumes of the CD cavity and surfactant (either the tail or in special cases the head group) are similar in magnitude. This will also be critically reviewed.

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1. An introduction to cyclodextrins and surfactants

Cyclodextrins (*CD*s) are a series of cyclic oligosaccharides formed through α(1–4) ether linkages of glucopyranose units [1,2]. The most commonly used *CD*s are the α-, β- and γ-cyclodextrins, having six, seven and eight glucoside unities, respectively. Among them, β-*CD* is the most commonly used, due to the relative ease of synthesis, low price and also to the size of its internal cavity into which a large number of guest molecules will fit. However, β-*CD* has a major drawback: the low solubility in water when compared with α- and γ-*CD*s. This is often discussed in terms of the relatively strong binding of β-*CD* molecules in the crystal state [3] and intramolecular hydrogen bond within the β-*CD* ring, preventing their hydrogen bond formation with surrounding water molecules [4,5]. *CD*s have the shape of a truncated cone with internal cavities ranging from 5 to 8 Å. The C–H bonds on the ring point inward producing a hydrophobic cavity. The nonbonding electron pairs of the glycosidic oxygen bridges are directed toward the inside of the cavity, producing a high electron density and lending it some Lewis base character. The primary and the secondary hydroxyl groups are located on the narrow and wide rims, respectively, of the truncated cone [6]. As a result of this spatial arrangement of the functional groups in the cyclodextrin molecules, the cavity shows a relatively hydrophobic character while the external surfaces are hydrophilic.

Although the synthesis of cyclodextrins was initially reported in 1891 by Villiers [7], it was only after the works of Schardinger [8], in the first decade of the 20th century, and of Szejtli, in the 1970s [9], that these molecules become popular among the scientific community. The number of publications dealing with various aspects of cyclodextrins have increased ca. 40% in the last decade (2002–2012) when compared with the previous decade (*Web of Science*®, accessed at 20.12.2012). Such attractiveness is justified by the ability of cyclodextrins' cavity to include a large range of guest molecules, such as drugs [10–17], surfactants [18–22], dyes [23–28], polymers [29–31] and inorganic salts [32–37], while the hydrophilic exterior renders *CD*s water soluble [38].

Cyclodextrin host–guest complexes may impart beneficial modifications of the properties of guest molecules such as solubility enhancement [39–41], stabilization of labile guests [42–44], physical isolation of incompatible compounds and control of volatility and sublimation [45–47]. These properties, complemented with their non-toxicity toward humans, make these molecules highly suitable for a large range of applications [48], including food technology [49,50], pharmaceutical and biomedicals [5,29,51–55], cosmetics [56,57], textile [58–62], analytical chemistry [63–65], chemical synthesis and catalysis [66–72], waste water and soil treatment [73–79], and corrosion coatings [80–82].

Cyclodextrins are also important in the context of the control of thickening of hydrophobically modified polymers, e.g., ethyl(hydroxyl ethyl) cellulose and modified poly(ethylene glycol) in water, by decoupling hydrophobic–hydrophobic intermolecular interactions [83–85].

Recently, Lindman et al. have shown that β- [86], 2-hydroxypropyl-β- [87], and α-cyclodextrins [88] can be efficiently used for decompaction of DNA–cationic surfactant complexes [89], on account of the high strength of the specific surfactant–cyclodextrin interactions, when compared with surfactant–DNA interactions. Similar studies were then carried out with *CD*–DNA–lipid systems [90,91]. The formation of inclusion compounds between *CD* and lipids allows one to control lipids self-assembly and, consequently, the DNA compaction/decompaction process.

The formation of the host–guest supramolecular complexes involving an amphiphilic compound and a cyclodextrin is driven by non-covalent interactions, including van der Waals, hydrophobic, electrostatic and charge transfer interactions, metal coordination, hydrogen bonding and steric effects [92,93]. The formation of these host–guest complexes allows one, by tunning the amphiphilicity of guest molecules, to control the assembly and disassembly of the supramolecular structure [93]. In aqueous solutions, the inclusion of the (dehydrated) guest into the non-polar cavity of the *CD* is accompanied by the release of water from the *CD* cavity. The latter process is strongly dependent on the interactions between water–water and water–cyclodextrin occurring inside the cyclodextrin cavity [94–96], and it also depends on other factors, including the size of both the cyclodextrin cavity and guest as well as the structure (geometry) of guest molecules [97,98].

Another factor that may influence the formation of host–guest compounds is the self-aggregation of *CD* in water [99–101]. It is however unclear how large fraction of the *CD* takes part in the aggregation. Some papers report mass contributions of aggregates in α-, β- or γ-*CD* aqueous solution of 0.001%, 0.0011% and 0.02% for initial concentrations of 12, 10 and 12 mM, respectively [102,103]. These low fractions of aggregated *CD* could explain why there are no evidences of aggregates as seen by ^{1}H NMR self-diffusion [104] or intermolecular diffusion, since these methods monitor the entire *CD* population [105–107]. If *CD* aggregation occurs, the evaluation of the binding constants in cyclodextrin-containing supramolecular structures becomes rather complicated.

Although much of the discussion on the host–guest association is based on the interactions between the guest and cyclodextrin cavity, the role of the hydrophilic part of cyclodextrin cannot be neglected [108]. For example, interactions between gemini surfactants and β-cyclodextrin appear to be affected by the hydrophilic part of the cyclodextrin [19]; on the other hand, the hydration shell of the highly soluble calcium lactate decreases in the presence of cyclodextrins [109], suggesting that *CD* has a structure-making effect on water [4].

Surfactants are of particular interest as guest molecules due to the balance of several intermolecular forces: the hydrophobic effect which tends to protect the tail from the aqueous environment, the requirement of dehydration of tails and head groups during complex formation, as well as effects due to steric hindrances. Surfactants also allow for carrying out systematic studies on the association (binding) process, by changing the surfactant structure and thus achieving a necessary balance between hydrophilic and hydrophobic contributions. This generally leads to changes in the physicochemical properties of surfactants, such as, e.g., the critical micelle concentration, of crucial importance for commercial formulations [110,111], from detergents and cleaners to cosmetics including detergency and personal care products [112,113].

The effect of *CD*s in micelle-containing amphiphilic solutions or in surfactant multicomponent systems (e.g., cationic/anionic surfactant–cyclodextrin mixed systems [114–118]), normally characterized by multiple competitive equilibria, is outside the scope of the present review; however, several interesting and significant works in this area have recently been published [21,119,120].

In this review we will focus on several aspects related to surfactant–cyclodextrin host–guest association including fundamentals, drawbacks and advantages of techniques commonly used to obtain insights on the structural and bulk solution changes resulting from host–guest association mechanism, and corresponding methods for binding quantification, as well as to carry out a critical assessment on different systems involving surfactants and natural cyclodextrins.

2. Techniques for measuring association between cyclodextrins and surfactants

Mixed cyclodextrin–surfactant systems have been studied not only from the point of view of fundamental issues but also on account of their role in practical applications. Host–guest interactions lead to measurable changes in physical-chemistry properties of the corresponding systems and thus, depending on the techniques used, structural and thermodynamic information on the binding process can be obtained. According to Mwakibete et al. [121], and recently reviewed by Brocos et al. [122], the available experimental techniques can be subdivided