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Cyclodextrin as a Template for Molecular Assembly: Formation of Heterodimers Between a Polyamino- and a Polysulfonato-β-Cyclodextrin

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Abstract. A poly(hydroxyethylamino)- and a poly(sulfonatophenyloxy)-β-cyclodextrin derivative, bearing opposite ionic charges, have been shown by potentiometric titration to form stable pH-dependent heterodimers with each other in water. The formation constants of these dimers show that a very stable assembly is formed between the fully deprotonated sulfonato derivative and the fully protonated amino derivative ($\log K_a$ = 8.5), which constitutes the assembly of multiple extended atomic groupings on cyclodextrin as template.

Key words: Polyamino-cyclodextrin, polysulfonato-cyclodextrin, cyclodextrin heterodimer

1. Introduction

Supramolecular assemblies involving cyclomalto-oligosaccharides (cyclodextrins) [1] have mostly made use of the host-molecular properties of these compounds [2]. Threaded rotaxanes [3] and nanotubular structures [4] involving cyclodextrins rely on the insertion of guest molecules into the hydrophobic cavities, in arrangements where the guest acts as a template and the host cyclodextrin is ordered on the threaded template [2, 5]. Small numbers of molecules have been assembled either within the cavity, as demonstrated by multi-guest complexes[1], or on the cavity rim when the cyclodextrin is used as an artificial catalyst [6]. In contrast, self-organisation of cyclodextrins without guests, leading to Langmuir layers [7], liquid crystals [8], or micelles [9], has been brought about by their conversion to glycolipids through covalent attachment of hydrophobic chains to the (externally) hydrophilic cyclodextrin as headgroup.

The concept of cyclodextrins as templates for the ordering of multiple large atomic groupings has not been tested to date. Arrays on the cyclodextrin would be circular, in multiples of six, seven or eight for the most common cyclodextrins, with potential for high-multiple branching [10]. The reported dimerisation of charged

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cyclodextrins in a complex with lead [11], and of oppositely charged amino and thiocarboxy cyclodextrins [12], leads to the conclusion that electrostatic forces could be used to array the templated molecules on the host's surface.

Here we show that extended structures on the rims of two β-cyclodextrins (**1**) and (**2**) can be brought to interact and form a circular array, formed by the strong electrostatic interaction between the seven aromatic anionic groups on one torus, and the seven hydroxyethylamino cationic groups on the other.

2. Experimental

Heptakis(6-hydroxyethylamino-6-deoxy)-β-cyclodextrin (**1**) (CD-EA) was synthesised as previously described [10]. Heptakis(6-sulfonatophenyloxy-6-deoxy)-β-cyclodextrin (**2**) (CD-BS) was synthesised by reaction of 4-hydroxyphenylsulfonic acid disodium salt with heptakis(6-bromo-6-deoxy)-β-cyclodextrin under conditions similar to those used by us already to glycosylate cyclodextrin [13]. The structure was confirmed by NMR spectroscopy (Varian Unity 500 MHz), and by FABMS (Thermoquest LCQ ion-trap spectrometer). Potentiometric titrations of protonated **1** in the presence of an equimolar quantity of **2**, were conducted in water at 25 °C I = 0.1M NaCl) to detect the formation of possible complexes and determine their stability. The procedure has previously been described by us [14]. Potentiometric data were treated with the programme Hyperquad [15].

The protonation constants of CD-EA have been measured previously [14], and full dissociation of CD-BS was confirmed.

3. Results and Discussion

The experimental potentiometric titration curve was compared to the simulated titration curve of a mixture of the compounds CD-EA and CD-BS assuming no interaction between them (Figure 1). A significant deviation of the experimental curve in the pH region 5–9 was observed, supporting the concept of ionic interaction between the two CDs.

In order to obtain a fit of the experimental points, new equilibria describing the interaction of protonated forms of CD-EA with CD-BS were introduced, assuming that a 1 : 1 stoichiometry would be the most probable. A satisfactory fit was found after the introduction of five heterodimers of the general formula $(EA)(BS)H_i$, i=2,3,5,6,7. The distribution curves of the dimers versus pH are shown on Figure 2. The percentage of formation generally decreases as the global charge of the species is increased.

The logarithms of the overall (β) and stepwise (K) stability constants of these heterodimers are given in Table I. It should be mentioned that the existence of other species is not excluded but could not be detected.

The stability of the dimers increases with the protonation degree of CD-EA. The most stable dimer, as expected, is formed between the fully protonated CD-

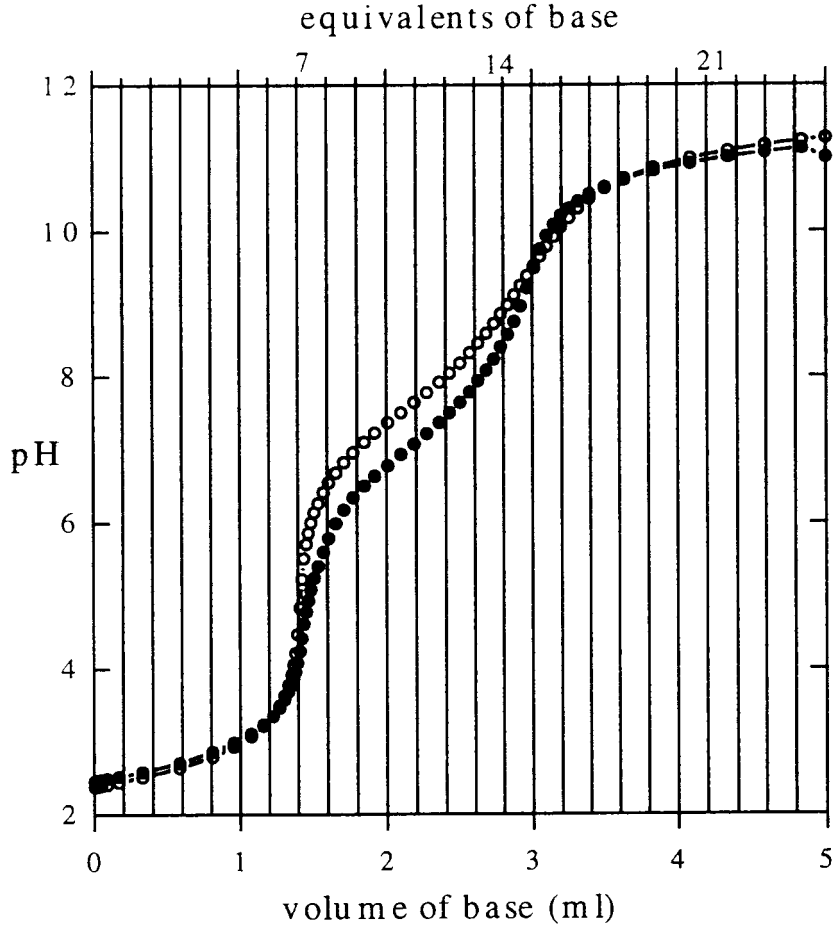


Figure 1. Titration curve of a 1 : 1 mixture of CD-EA and CD-BS (5×10^{-4} M) by NaOH (2.42×10^{-2} M) (○) and simulated titration curve without interaction between the two CDs (●).

EA (LH_7^{7+}) and the heptasulfonato CD-BS, consistent with maximal electrostatic interaction. The resulting species is neutral in charge and, because of the similar circular distribution of the charges on each CD, may reasonably be considered as a face-to-face dimer.

Proton NMR (270 MHz in D_2O—HCl, pD4) was used to compare the environments of the complexed and uncomplexed ions, and in particular to confirm interactions within the aromatic and alkylamino arrays. Significant chemical shift changes $\Delta\delta$ were observed with equimolar mixed solutions of **1** and **2** as compared with the pure solutions at the same pH. Values of $\Delta\delta$ were as follows: -0.08 (aromatic protons of **2**), -0.08 (CH_2OH), -0.07 (anomeric protons of **1**), -0.16 ppm (anomeric protons of **2**). Such changes are unknown for side-chain protons, with a

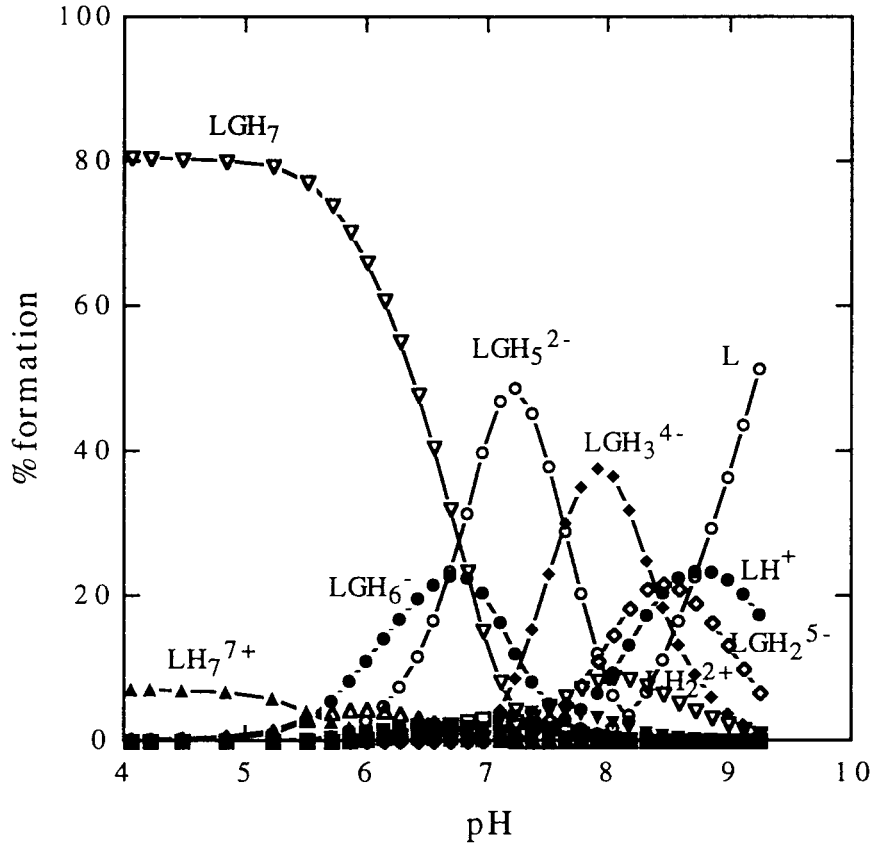


Figure 2. Distribution curves of the heterodimers versus pH.

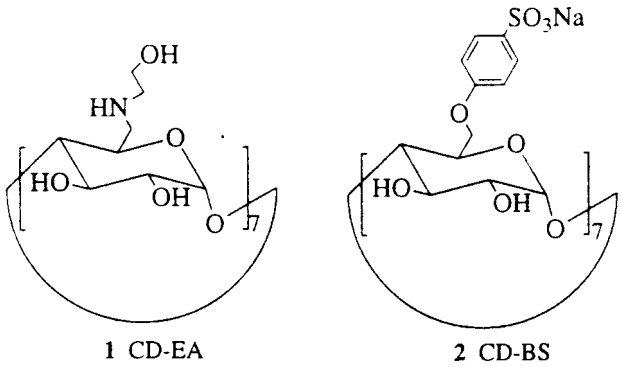
few exceptions where the side-chains are involved in complexation [16]. The $\Delta\delta$ values for anomeric protons indicate changes in the overall conformations of the cyclodextrins by rotation about the glycosidic links [17], and also are normally not observed on inclusion complexation.

These NMR changes in the complex exclude configurations where, by analogy with other substituted cyclodextrins [18] and cyclodextrin-nucleotide complexes [19], an aromatic ring of CD-BS is included in the cavity of CD-EA from the secondary-hydroxyl side, with interaction between the sulphonato group of the first CD and the amino groups of the second. An inclusion complex would show chemical shift changes for the H-3 and H-5 atoms of the host molecule. These are the cavity-oriented protons which are usually used to diagnose guest inclusion, and are particularly affected by inclusion of aromatic guests. No significant change is observed for these protons in complexed CD-EA.

The stability of the neutral heterodimer, although high ($\log K$ = 8.5), is lower than that reported for the heptazwitterionic heterodimer formed between β-cyclodextrin derivatives bearing respectively seven primary amino groups and

Table I. Logarithms (with standard deviations) of the overall (β) and stepwise (K) stability constants of the complexes of CD-EA (L) with CD-BS (G) (I = 0.1 M; 25 °C). Charges are omitted for simplicity.

$L + G + 2H \rightleftharpoons LGH_2$	21.3(3)
$L + G + 3H \rightleftharpoons LGH_3$	29.5(2)
$L + G + 5H \rightleftharpoons LGH_5$	44.9(3)
$L + G + 6H \rightleftharpoons LGH_6$	51.8(2)
$L + G + 7H \rightleftharpoons LGH_7$	58.6(4)
$LH_2 + G \rightleftharpoons LGH_2$	4.4(3)
$LH_3 + G \rightleftharpoons LGH_3$	5.3(2)
$LH_5 + G \rightleftharpoons LGH_5$	7.0(3)
$LH_6 + G \rightleftharpoons LGH_6$	7.2(6)
$LH_7 + G \rightleftharpoons LGH_7$	8.5(4)



1 CD-EA 2 CD-BS

Figure 3.

seven thiocarboxylate groups ($\log K = 10.25$) [12]. There is obviously an unfavourable effect due to the interacting charges on one cyclodextrin being on the aromatic-group extension rather than on the more fixed circumference of the cyclodextrin face. However the principle has been established that substantial atomic groupings on the cyclodextrin as template can be arranged for interaction to form circular molecular assemblies. We have shown already that the presence of multiple hydrophobic chains on the cavity influences complexation by cyclodextrins, since they form an extension of the cavity on the more hydrophobic side [8]. It is possible that the hydroxyethyl and aromatic groupings in the present modified cyclodextrins also aid the polar interactions by providing a less aqueous environment.

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