Heat Capacities of Hydroxypropyl-α-, -*β*-, and -*γ*-Cyclodextrins in Dilute Aqueous Solution

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Apparent molar heat capacities of the hydroxypropyl-α-cyclodextrin, hydroxypropyl-*β*-cyclodextrin, and hydroxypropyl-*γ*-cyclodextrin in aqueous solution have been determined at 298.15 K allowing the evaluation of their heat capacities at infinite dilution in water. The calorimetric data do not indicate evidence of aggregation of the hydroxypropylcyclodextrins. The differences in behavior of these modified cyclodextrins compared to linear oligosaccharides, and native cyclodextrins are analyzed.

Introduction

Naturally occurring cyclodextrins (CD) are homochiral cyclic oligosaccharides composed of 6, 7, or 8 α-1,4-linked D-glucopyranose units, called α-cyclodextrin (αCD), *β*-cyclodextrin (*β*CD), and *γ*-cyclodextrin (*γ*-CD), respectively. They are produced through the degradation of starch by the enzyme CD-glucosyltransferase.[1] They possess a hydrophobic cavity which makes them suitable for the formation of inclusion complexes. The CDs contain 18 (αCD), 21 (*β*CD), or 24 (*γ*CD) hydroxyl groups, which can be modified chemically. Native CDs have been modified for a variety of reasons ranging from achieving solubility in a desired solvent to investigating the mechanisms of enzyme-catalyzed reactions.[2] Several classes of compounds which can be included in native CDs have been subjected to systematic thermodynamics studies, however there are only a few studies using modified CDs.[3] It has been shown that the heat capacities for these sugars are significantly larger than would be expected from calculations using an empirical additive scheme.[4] At least in part is this due to the lack of accurate heat capacities data for the modified CD's.

On reacting *β*CD in alkaline solution with propylene oxide, a 2-hydroxypropyl group will be connected to one or more hydroxyls of the *β*CD. The degree of substitution characterizes such a heterogeneous product, and this can be expressed as the average molar substitution (MS), the number of the hydroxypropyl groups per glucose unit.[5]

In this study, we investigated the apparent molar heat capacity, $C_{p\phi 1}$, for the hydroxypropyl-α-cyclodextrin (HPαCD) and hydroxypropyl-*γ*-cyclodextrin (HP*γ*CD) with MS = 0.6 and hydroxypropyl-*β*-cyclodextrin (HP*β*CD) with MS = 0.6, 0.8, and 1.0 in aqueous solution at infinite dilution. This means, for instance, that one molecule of HP*β*CD, formed by 7 glucopyranose units, contains on average 4.2 hydroxypropyl groups when MS = 0.6 and its molecular weight (MW) is 1380 g mol^{-1}.

Experimental Section

Apparatus and Procedure. Volumetric heat capacities were measured at 298.15 K using a Picker flow microcalorimeter (Sodev, Inc., Canada) with the procedures described in the literature;[6,7] the uncertainty for the volumetric heat capacity is 1×10^{-4} J K^{-1} cm^{-3}. The volumetric heat capacities were converted into molar heat capacities using densities obtained with a vibrating-cell densimeter model 03-D (Sodev, Inc., Canada) taking distilled, deionized, and degasified water (Barnstead Nanopure Infinity, with a resistivity of 18 MΩ cm) (0.99705 g cm^{-3})[8] and carbon tetrachloride (1.58436 g cm^{-3}) as references.[9] The uncertainty is 1×10^{-5} g cm^{-3}. The calorimeter and the densimeter were connected in series, and their temperature was controlled to ±0.003 K using a CT-L thermostat (Sodev, Inc.). The heat capacity of solutions was determined using water as the reference liquid (C_p = 75.315 J K^{-1} mol^{-1}).[7] The reproducibility of the results, under nominally identical experimental conditions, was between 1.5 and 4% of the heat capacity depending on the system.

Materials. The modified cyclodextrins were purchased from Aldrich. These materials were of the highest purity available and were used without further purification. Solutions were prepared by mass (Mettler AT250). The uncertainty in the mole fraction weighing was $\pm 1 \times 10^{-5}$. To take into account the hydration of the CD in the preparation of the solutions, the water content of the samples was determined by the Karl-Fisher method (701 KF Titrino, Metrohm, Swiss) using Hydranal Composite 5 reagent from Sigma-Aldrich and giving the following values: HPαCD (5.27 ± 0.08)H_2O (MS = 0.6, MW = 1180 g mol^{-1}); HP*β*CD (4.49 ± 0.21)H_2O (MS = 0.6, MW = 1380 g mol^{-1}); HP*β*CD (4.45 ± 0.22)H_2O (MS = 0.8, MW = 1460 g mol^{-1}); HP*β*CD (4.47 ± 0.09)H_2O (MS = 1.0, MW = 1540 g mol^{-1}); HP*γ*CD (5.39 ± 0.08)H_2O (MS = 0.6, MW = 1580 g mol^{-1}).

Results and Discussion

The apparent molar heat capacities, $C_{p\phi 1}$, of CDs (component 1) can be calculated using

$$C_{p\phi 1} = \frac{C_p(\text{sol}) - x_2 C_{p2}{}^0}{x_1}$$

where C_p(sol) is the molar heat capacity of the solution, x_1 is the molar fraction of the CD in the solution, $C_{p2}{}^0$ is the molar heat capacity of the pure water, and x_2 its molar

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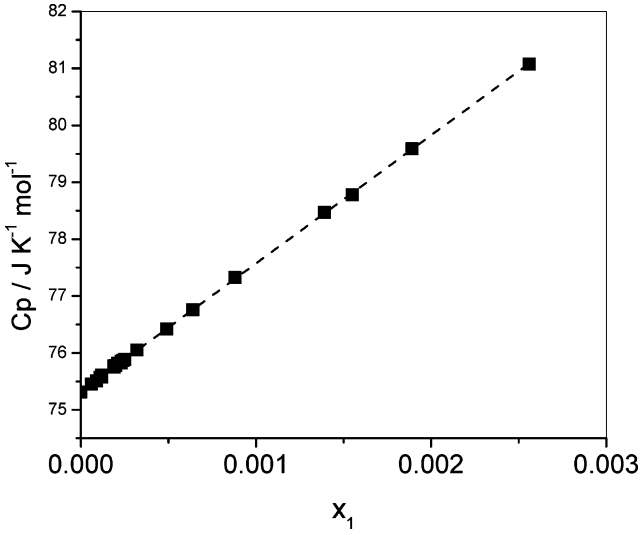

Figure 1. Apparent molar heat capacity for HPαCD, C_p, as a function of its molar fraction in aqueous solution, x_1 at 298.15 K. The linear fitting gives $C_{p1} = \{75.322(\pm 0.004) + (2252 \pm 5)x_1\}$/J K^{-1} mol^{-1} with $R = 0.999$.

Table 1. Apparent Molar Heat Capacities of the Cyclodextrins in Aqueous Solution at Infinite Dilution, $C^{\infty}_{p\phi 1}$

solute	g^a	MS^a	$C^{\infty}_{p\phi 1}$/J·K^{-1}·mol^{-1}
HPαCD	6	0.6	2327 ± 5
HPβCD	7	0.6	2633 ± 8
HPβCD	7	0.8	3070 ± 21
HPβCD	7	1.0	3394 ± 15
HPγCD	8	0.6	3103 ± 8

[a] g is the number of glucose units, and MS is the molecular substitution.

fraction in the solution. When we tried to use this equation to calculate $C_{p\phi 1}$ for very dilute cyclodextrins aqueous solutions, we found that the problem is that the uncertainty is enormous due to the dispersions of the data at $x < 0.0005$; then, we looked for another method to calculate them and it is explained below.

Figure 1 shows C_p(sol) for HPαCD as function on its molar fraction x_1. It is clear that there is a linear dependence of C_p(sol) on molar fraction; in this case, the linear fitting gives $C_{p1} = \{75.322(\pm 0.004) + (2252 \pm 5)x_1\}$/J K^{-1} mol^{-1} with $R = 0.999$. Similar results were found for all the systems studied here, therefore; in general, C_p(sol) = $C_{p2}{}^0 + bx_1$, where b is the slope of the straight line and $C_{p\phi 1}$ can be obtained like

$$C_{p\phi 1} = \frac{C_{p2}{}^0 + bx_1 - x_2 C_{p2}{}^0}{x_1}$$

$$C_{p\phi 1} = C_{p2}{}^0 + b$$

This result implies that $C_{p\phi 1}$ is independent of concentration, then $C_{p\phi 1} = C^{\infty}_{p\phi 1}$. This is true for the systems we studied here at least at low concentrations. In the case of HPαCD, $C^{\infty}_{p\phi 1} = (75.315 + 2252)$/J K^{-1} mol^{-1}. In this work, all $C^{\infty}_{p\phi 1}$ values were calculated following this procedure; to test it, $C^{\infty}_{p\phi 1}$ for native αCD was determined. The value we found (1482 ± 7 J K^{-1} mol^{-1}) was in fair agreement with that reported in the literature (1481 ± 11 J K^{-1} mol^{-1}).[4]

Table 1 shows the apparent molar heat capacities, $C^{\infty}_{p\phi 1}$, of the HPCDs in dilute aqueous solution. Tables 2−6 show

Table 2. Experimental Density and Heat Capacity for the HPαCD (MS = 0.6) (1) + Water (2) System

$10^3 x_1$	ρ/g·cm^{-3}	C_p/J·K^{-1}·mol^{-1}
0.06	0.99831	75.45
0.09	0.99903	75.51
0.09	0.99894	75.51
0.11	0.99951	75.57
0.12	0.99965	75.57
0.12	0.99983	75.61
0.19	1.00117	75.75
0.19	1.00135	75.77
0.20	1.00146	75.78
0.21	1.00177	75.82
0.23	1.00211	75.82
0.23	1.00218	75.82
0.23	1.00221	75.85
0.24	1.00253	75.87
0.25	1.00251	75.88
0.25	1.00264	75.89
0.32	1.00402	76.05
0.49	1.00711	76.42
0.64	1.01032	76.76
0.88	1.01495	77.33
1.39	1.02471	78.47
1.55	1.02819	78.78
1.89	1.03385	79.59
2.56	1.04564	81.08

Table 3. Experimental Density and Heat Capacity for the HPβCD (MS = 0.6) (1) + Water (2) System

$10^3 x_1$	ρ/g·cm^{-3}	C_p/J·K^{-1}·mol^{-1}
0.15	1.00106	75.71
0.17	1.00145	75.75
0.19	1.00206	75.82
0.21	1.00244	75.86
0.25	1.00342	75.96
0.31	1.00476	76.16
0.32	1.00545	76.16
0.34	1.00584	76.22
0.37	1.00636	76.29
0.37	1.00637	76.27
0.38	1.00662	76.29
0.40	1.00711	76.34
0.43	1.00785	76.42
0.45	1.00837	76.47
0.49	1.00932	76.57
0.51	1.00981	76.63
0.55	1.011	76.71
0.59	1.01208	76.84
0.65	1.01326	76.99
0.66	1.0135	77.01
0.77	1.01628	77.27
0.83	1.01768	77.45
0.91	1.0198	77.62
1.09	1.02412	78.13
1.15	1.02556	78.27
1.22	1.02702	78.45
1.28	1.02875	78.60
1.29	1.02863	78.64

experimental density and heat capacity for all the HPCDs in aqueous solutions studied in this work.

Figure 2 shows $C^{\infty}_{p\phi 1}$ values plotted against a number of glucose units (g) for oligosaccharides and native CDs from the literature[4] and for the HPCDs with MS = 0.6 reported in this work. The $C^{\infty}_{p\phi 1}$ values increase linearly with the number of glucose units. Three straight lines are obtained. They represent the behavior of the three different kinds of oligosaccharides (linear oligosaccharides, native CDs, and HPCDs). The difference could be considered to be due partly to the loss of water when the CD rings are formed, partly to the more rigid structure of the ring-shaped molecules[4] and, in the case of the modified CDs, also to the contribution of the hydroxypropyl group, which means that the lines representing the behavior of native and

Table 4. Experimental Density and Heat Capacity for the HPβCD (MS = 0.8) (1) + Water (2) System

10^3x_1	ρ/g·cm^{-3}	C_p/J·K^{-1}·mol^{-1}
0.13	1.00044	75.71
0.17	1.00125	75.83
0.19	1.00174	75.89
0.20	1.00199	75.92
0.22	1.00260	75.98
0.30	1.00444	76.22
0.40	1.00694	76.49
0.41	1.00666	76.49
0.45	1.00840	76.67
0.48	1.00838	76.70
0.51	1.00992	76.82
0.51	1.0096	76.85
0.58	1.01146	77.06
0.72	1.01472	77.48
0.78	1.01624	77.66
0.94	1.02017	78.14

Table 5. Experimental Density and Heat Capacity for HPβCD (MS = 1.0) (1) + Water (2) System

10^3x_1	ρ/g·cm^{-3}	C_p/J·K^{-1}·mol^{-1}
0.05	0.99812	75.49
0.06	0.99866	75.54
0.09	0.99931	75.66
0.09	0.99904	75.62
0.12	1.00017	75.76
0.14	1.00064	75.81
0.15	1.00087	75.86
0.15	1.00087	75.86
0.17	1.00109	75.90
0.18	1.00146	75.94
0.20	1.00189	75.99
0.28	1.00374	76.28
0.30	1.00439	76.40
0.32	1.00506	76.43
0.36	1.00586	76.57
0.38	1.00629	76.67
0.38	1.00621	76.62
0.43	1.00761	76.79
0.48	1.00904	76.93
0.49	1.00876	76.99
0.51	1.00916	77.12
0.57	1.01065	77.34
0.57	1.01061	77.25
0.63	1.01215	77.57
0.71	1.0139	77.85
0.73	1.01427	77.92
0.81	1.01662	78.06
0.87	1.01757	78.25
0.90	1.01882	78.32
0.96	1.01966	78.54
1.08	1.0231	78.92
1.34	1.02874	79.80
1.4	1.02987	80.00
1.71	1.0367	81.00
1.77	1.03846	81.23
1.88	1.04023	81.56

hydroxypropyl CDs are not parallel. The linear fitting for the modified CDs gives a slope of (388 ± 47) J K^{-1} mol^{-1}, this is the contribution of one hydroxypropyl-glucopyranose (MS = 0.6) ring in the HPCDs.

Figure 3 shows the $C^{\infty}_{p\phi 1}$ values plotted against MS for the HPβCD. The linear fitting gives $C^{\infty}_{p\phi 1}$ = {1510(±133) + 1903(±166)(MS)}/J K^{-1} mol^{-1}, hence the contribution of one hydroxypropyl group in a glucopyranose unit is 1903/7 J K^{-1} mol^{-1}, where 7 is the number of glucopyranose units in this CD. The value of $C^{\infty}_{p\phi 1}$ extrapolated to MS = 0 for the HPβCDs does not correspond to that for the native βCD, but it is closer to that for the native αCD. This could be understood considering that, when one molecule of HPβCD (MS = 0.6) is formed, 3.6 hydroxyl groups are substituted by hydroxypropyl groups and therefore the resulting modi-

Table 6. Experimental Density and Heat Capacity for the HPγCD (MS = 0.6) (1) + Water (2) System

10^3x_1	ρ/g·cm^{-3}	C_p/J·K^{-1}·mol^{-1}
0.02	0.99785	75.38
0.04	0.99843	75.44
0.05	0.9986	75.45
0.05	0.99866	75.46
0.06	0.99907	75.50
0.06	0.99914	75.51
0.07	0.99927	75.52
0.08	0.9995	75.54
0.11	1.0004	75.63
0.11	1.00053	75.65
0.12	1.00083	75.68
0.18	1.00256	75.85
0.19	1.00294	75.89
0.26	1.00496	76.09
0.31	1.00645	76.24
0.36	1.00818	76.42
0.57	1.01445	77.05
0.70	1.01814	77.42
0.77	1.02051	77.66
0.89	1.02399	78.01
1.05	1.0287	78.48

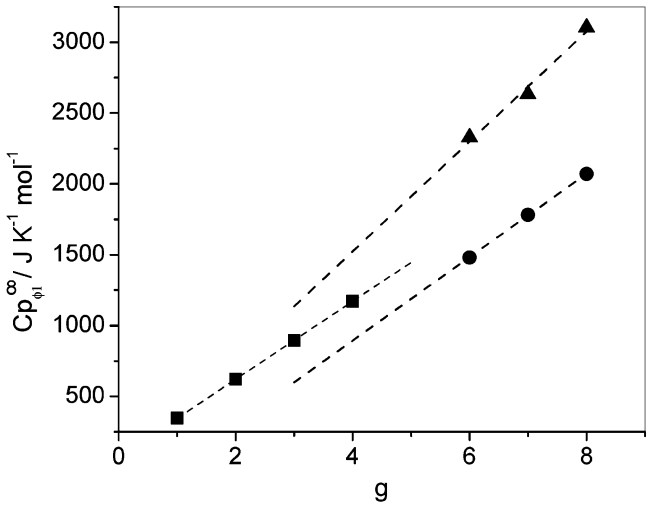

Figure 2. Apparent molar heat capacity at infinite dilution, $C^{\infty}_{p\phi 1}$, for: glucose oligosaccharides, ■; native cyclodextrins, ●; hydroxypropyl cyclodextrins, ▲; as a function of glucose units, *g*.

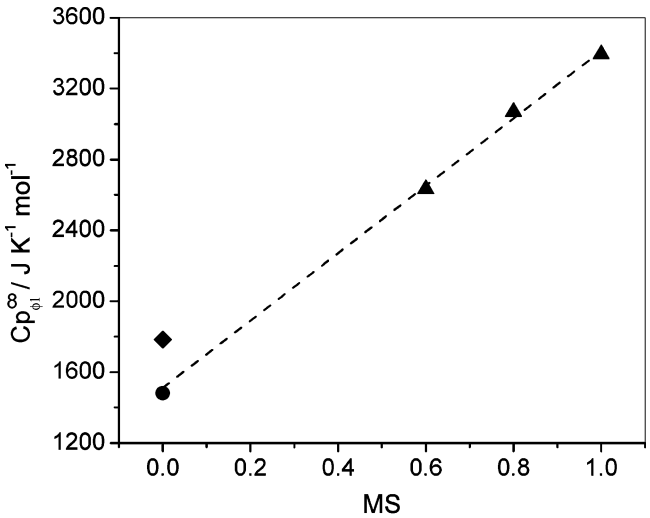

Figure 3. Apparent molar heat capacity at infinite dilution, $C^{\infty}_{p\phi 1}$, for the HPβCD at infinite dilution as a function of molar substitution (MS) ▲; αCD, ●; and βCD, ◆.

fied CD with MS → 0 has a structure that is closer to the native αCD which has less OH groups compared to the native βCD.

There are several studies in the literature[10−13] that report sharp changes in the properties of CD at certain concentrations. This is the typical behavior of a system that shows aggregation phenomena.[14] The heat capacity data in this work do not reflect this aggregation behavior.

Conclusion

The calorimetric study of the HPCDs in water does not give any evidence of aggregation. The differences in the behavior found among linear oligosaccharides, native CDs, and HPCDs could be attributed partly to the loss of water, partly to the more rigid structure of the ring-shaped molecules, and, in the case of the modified CD's, to the contribution of the hydroxypropyl group.

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