Thermodynamics of the interactions of ascorbic acid with α- and β-cyclodextrins in aqueous solutions

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As found by calorimetry and densimetry, ascorbic acid forms a molecular 1:1 complex with α- but not with β-cyclodextrin in aqueous solution.

The role of ascorbic acid (AA) (vitamin C) in biochemical processes is well known.[1] The products of ascorbic acid oxidation are toxic and undesirable to health.[2,3] Therefore, increasing the stability of a biologically active form of ascorbic acid is a topical problem.

Cyclodextrins (CDs) can be used for the encapsulation of vitamin C to increase its stability. CDs are capable to include guest molecules in the hydrophobic internal cavity, thus protecting them from the influence of external factors.[4]

This problem was considered in a few publications.[5–8] It was found that the presence of β-CD enhances the fluorescence of ascorbic acid in an alkaline medium because of inclusion complex formation.[5] Manzanares *et al.*[7,8] found that the inclusion of ascorbic acid in β-CD in an acidic medium increases the stability of ascorbic acid to oxidation, and no effect was observed with α-CD.

The aim of this work was to study the ability of CDs to complexation with ascorbic acid in aqueous solutions.

The enthalpies of dissolution of α- and β-CDs† in twice-distilled water and freshly prepared aqueous solutions of ascorbic acid‡ (concentration of 0.05–0.35 mol kg^{-1}) were measured[9] using an isothermal calorimeter at 298.15 K. The CD concentration was constant [(1.10±0.05)×10^{-3} mol kg^{-1}]. The error in the heats of dissolution was 0.03 J (< 5%).

The experimental enthalpies of dissolution formed a basis for calculation of the enthalpic coefficients of pair interactions (h_{xy}) of CD with ascorbic acid according to the MacMillan–Mayer formalism in the case of weak interactions;[10,11] and thermodynamic functions lg K, $\Delta_c G^0$, $\Delta_c H^0$, $\Delta_c S^0$, in the case of complex formation[12] (Table 1). The conceivable processes of CD and ascorbic acid dissociation were taken into consideration.[13,14] For this purpose, the thermodynamic characteristics of dissociation reactions[13,14] were taken into account using the HEAT computer program for calculating lg K and $\Delta_c H^0$.

The densities of solutions were measured at 298.15±0.005 K with a bicapillary pycnometers calibrated with water.[15] The measurements error was not greater than 3×10^{-5} g cm^{-3}. The apparent molar volumes of CDs ($V_{\phi,\,CD}$) in water and in aqueous ascorbic acid solutions (concentrations of 0.0025–0.017 mol kg^{-1}) were evaluated. For binary solutions (CD + H_2O), water was a reference solvent (ρ = 0.99705 g cm^{-3}), for ternary solutions (CD + + ascorbic acid + H_2O), an aqueous ascorbic acid solution of a particular concentration was a reference solvent.[16] The results are presented in Table 2.

Table 1 The enthalpic coefficients, equilibrium constants, free energies, enthalpies and entropies of interactions of ascorbic acid with α- and β-cyclodextrins in water at 298.15 K.[a]

System	h_{xy}/ kJ kg mol^{-2}	K/kg mol^{-1}	$\Delta_c G^0$/ kJ mol^{-1}	$\Delta_c H^0$/ kJ mol^{-1}	$T\Delta_c S^0$/ kJ mol^{-1}
α-CD + ascorbic acid	—	1.9 (±0.2)	–1.6 (±0.3)	–6.0 (±0.3)	–4.3 (±0.7)
β-CD + ascorbic acid	–1.8 (±0.9)	—	—	—	—

[a]Standard deviations are given in parentheses.

Table 2 Apparent molar volumes of α- and β-cyclodextrins in aqueous solutions of ascorbic acid at 298.15 K.

m_{AA}/ mol kg^{-1}	$\rho_{AA + H_2O}$/ g cm^{-3}	m_{CD}/ mol kg^{-1}	$\rho_{AA + CD + H_2O}$/ g cm^{-3}	$V_{\phi,CD}$/ cm^3 mol^{-1}
		α-cyclodextrin		
0.000000	—	0.004979	0.99872	636.6
0.002602	0.99728	0.004948	0.99890	645.3
0.004989	0.99746	0.005073	0.99909	651.3
0.006936	0.99752	0.004972	0.99916	642.9
0.008125	0.99764	0.004965	0.99930	638.7
0.010115	0.99778	0.004982	0.99945	637.2
0.012785	0.99796	0.005002	0.99964	636.5
0.014927	0.99813	0.004980	0.99981	635.0
		β-cyclodextrin		
0.000000	—	0.004970	0.99920	701.1
0.002540	0.99726	0.005049	0.99945	700.4
0.004932	0.99745	0.005010	0.99960	705.0
0.006886	0.99756	0.004972	0.99971	701.7
0.008235	0.99765	0.004995	0.99981	701.7
0.009940	0.99779	0.004964	0.99992	705.0
0.011060	0.99788	0.004946	0.99999	707.5
0.015500	0.99814	0.004985	1.00028	704.7

The interaction of α-CD with ascorbic acid is accompanied by complex formation; the interaction of β-CD with ascorbic acid is weak, and a complex is not formed. This fact has experimental confirmations. In the α-CD + ascorbic acid system, the following was observed: (i) with an increase in ascorbic acid concentration, the measured thermal effects of solution of α-CD became approximately constant after a considerable decrease; (ii) the function $V_{\phi,\alpha\text{-CD}}(m_{AA})$ has a maximum corresponding to the stoichiometry of the complex.[16] In the case of weak interactions (system β-CD + ascorbic acid): (i) the thermal effects of dissolution were linear functions of ascorbic acid concentration, with small slopes; (ii) the function $V_{\phi,\beta\text{-CD}}(m_{AA})$ exhibited no extremums.

The enthalpic coefficient is negative for the β-CD + ascorbic acid system (Table 1). Coefficients h_{xy} provide information on the energetic relationship between solute–solute and solvent–solute interactions.[17] At $h_{xy} < 0$, it is possible to judge about the prevalence of the weak energetically favourable interactions of β-CD with ascorbic acid.

The complexation between α-CD and ascorbic acid in water is characterised by small negative values of enthalpy and entropy changes (Table 1). Thus, the complex is enthalpically stabilised.

Volumetric measurements were performed to define the stoichiometry of the complex. The maximal value of $V_{\phi,\alpha\text{-CD}}$ was observed at m_{AA} = 0.004989 mol kg^{-1} and $m_{\alpha\text{-CD}}$ = 0.005073 mol kg^{-1} (Table 2), which corresponds to the composition 1:1. Therefore, we treated the thermodynamic functions (Table 1) according to the following reaction:

$$\alpha\text{-CD} + AA \longrightarrow \alpha\text{-CD}\cdot AA + \Delta_c H^0.$$

† Commercial α- and β-CDs (Sigma) were used. The water content of β-CD was 13.7%, which was taken into account in the preparation of solutions.

‡ Ascorbic acid was additionally purified by recrystallization from water–ethanol and dried *in vacuo* at 333 K for 4 days before use.

Under the experimental conditions, the undissociated form of ascorbic acid (α = 96–99% for the ascorbic acid concentration used in calorimetry and α = 86–91% for densimetry) is predominant in solution. We believe that the undissociated form of ascorbic acid participates in the interactions with CD, and the molecular complex α-CD–ascorbic acid is formed.

The transfer volumes may be interpreted on the basis of a model of overlapping solute solvation shells.[18] With reference to volumetric properties, this model predicts an increase of the volume of the solute ($\Delta V_{tr} > 0$) if the interaction is due to hydrogen bonds, electrostatic forces *etc*. A decrease of the volume ($\Delta V_{tr} < 0$) occurs if the interaction is caused by nonpolar groups (hydrophobic forces). The volumes of transfer of α- and β-CDs from water to aqueous ascorbic acid solutions are positive (Table 2). Therefore we assume that H-bonds are formed between ascorbic acid and CDs.

It is well known that the complexes of CDs with guest molecules are formed due to hydrophobic and van der Waals forces and H-bonding.[4] Hydrophobic effects are characterised by small positive $\Delta_c H^0$ and $\Delta_c S^0$ values.[19] Based on data given in Table 1 and 2, we assumed that they do not play a predominant role in the complexation of α-CD with ascorbic acid. The driving forces of complex formation are the van der Waals interactions and hydrogen bonding. Thus, since the α-CD cavity is smaller than the β-CD cavity[20] and since van der Waals interactions depend on the distance of separation, it is necessary to expect stronger interaction of ascorbic acid with α-CD than with β-CD. The molecule of α-CD is more flexible;[21] therefore, it may change the conformation in a solution, being arranged, thus, for interaction with ascorbic acid more easily.

Note that the results are inconsistent with spectroscopic data.[7] The apparent stability constant for the 1:1 ascorbic acid–β-CD complex in an acidic medium (0.5 M H_2SO_4) was 269±10 dm^3 mol^{-1}. The spectroscopic determination of the stability constant of the corresponding complex with α-CD was impossible. The presence of an electrolyte may change the solvation and, consequently, the complexing properties of CDs to ascorbic acid. The formation of ascorbic acid–α-CD in pure water was confirmed by calorimetry and densimetry.

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